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PRESIDENTIAL ADDRESS *

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IT has become one of the customs and traditions of the American College of Physicians each year to accord to the retiring President the privilege of formally addressing the society. As I undertake to fulfill this pleasant obligation I heartily wish that I possessed the sagacity and skill of the late Dr. Francis Delafield who, on the occasion of the first meeting of the Association of American Physicians, delivered an address that rivalled in completeness, wisdom and brevity the oft quoted Gettysburg speech of the immortal Lincoln. Dr. Delafield's remarks occupy a little short of one page of the transactions of the Association. Although I cannot hope to emulate his achievement I can, however, put your minds at rest with the assurance that I shall do my best not to trespass too long upon your time and patience in what I have to say.

The months that have intervened since our memorable Clinical Session in Montreal have been fraught with events of international as well as national importance. Unbelievable changes of political, social, economic and industrial significance have taken place. Every social group, physicians along with all others, has been profoundly affected. As the result of these altered conditions, the American College of Physicians, together with other organizations, has had to meet unusual and unexpected problems as well as unprecedented economic situations. It is with considerable pride, therefore, that we are able to come before you at this time secure in the knowledge that in spite of the difficult conditions that have existed, the American College of Physicians has thus far come through these turbulent times unscathed.

The losses from the ranks of our Fellows and Associates by death and resignation have been more than offset by the additions to our membership, so that today the total enrollment in the College is 3,100. Furthermore, none of the essential activities of the College has been given up or seriously curtailed. This satisfactory state of affairs is due in large measure to the excellent business judgment, alert watchfulness, and painstaking economy that has been exercised by your Executive Secretary in his efforts to manage the affairs of the College in strict accordance with the wise, far-sighted and

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conservative policies laid down for him by your Board of Regents and Board of Governors, all of whom richly merit your confidence and support. I wish to take advantage of this occasion to express to them my personal appreciation of the never-failing interest they have shown in the College and to thank them for the loyal and helpful support they have accorded me, without which your presiding officer would have been unable to direct the affairs of the society with any measure of success.

A survey of the addresses of some of my distinguished predecessors as President of the College, discloses the fact that it was not unusual in the past to devote considerable time to a justification of the College and its purposes. Such a discussion today is wholly superfluous in the light of the progress and achievements of the College during the past decade. No more convincing proof is needed that the College has amply justified its existence and now occupies a permanent and unique position among the medical organizations of this continent, than is afforded by an examination of the Roster of our Fellows. It now includes a very great number who, by reason of their outstanding accomplishments in various fields of internal medicine and allied medical sciences, have not only achieved distinction as clinicians and teachers, but have also contributed liberally to the great advances that have taken place in Clinical Medicine during the last quarter of a century.

If time were available it would be both interesting and profitable to enumerate the truly outstanding contributions to the progress of medicine that can be attributed to the Fellows of this College. Moreover, we are particularly fortunate not only in having Fellows who have been and are leaders in medical thought, but in being able to number among our membership a large group of younger Associates, many of whom have already, or soon will have acquired prominence as internists. In these Associates lie the real strength and scientific hope of the College. It is not enough for an organization to number among its members those who have attained distinction; if it would prosper and extend its influence it must be nourished by a steady influx of those who possess the potentialities for future accomplishment.

It has frequently been said that if the American College of Physicians had done nothing else than to inaugurate and successfully conduct its Annual Clinical Sessions, it would have amply justified its existence. With each succeeding year these Sessions have attained greater importance and greater scientific interest. They are unique in that they bring together from all parts of the country, under unusually auspicious conditions, the largest group of men who are primarily interested in all the many and varied aspects of Internal Medicine in its broadest sense.

As popular and successful as these meetings have become, we must not rest content with our present accomplishment. We must be constantly on the alert to find ways and means of improving these Clinical Sessions. Every effort should be put forth to have the outstanding work of the year

that is of interest to clinicians reviewed at our Sessions. In this way large and interested audiences will be assured. It is a well known fact that the prospect of an adequate and discriminating audience is a most effective stimulus to good scientific effort. If we consistently make such audiences available at our meetings, we shall provide an inspiring setting that will soon make those who are doing worthwhile work more eager to present the results of their labors before this College than elsewhere. The hope of having an opportunity to participate in the program of our Clinical Session should prove a constant stimulus to our Associate members. It is not too ambitious to look forward to the day when the gatherings of this College will hold such a conspicuous place among the medical meetings of America that the majority, at least, of the important advances in clinical medicine on this continent will be given to the world through the medium of the American College of Physicians.

It seems not inappropriate at this point to turn away from these questions that involve chiefly the interest and welfare of the College and consider for a moment certain problems that are of fundamental importance to the members of this College as well as to the medical profession as a whole.

Since the world became engulfed in a wave of economic and social unrest associated with widespread financial depression, a number of problems of sociologic, economic and even political importance in connection with medical practice have engaged the attention of the lay public as well as the medical profession of this country. Indeed, in some localities these problems seem to have transcended in importance and popular interest all other aspects of medicine. The term medical economics has sprung into prominence of late and has quite generally been adopted as an expression to designate those problems that involve the various relationships that exist or can arise between physicians, on the one hand, and the public and the state on the other. It is unnecessary to enumerate the manifold problems that fall into this category. Let me hasten to reassure you at this point that your speaker has no intention nor desire to open up the already much debated, although still far from settled problems of medical economics.

The importance of these questions to the country at large as well as to the medical profession is undeniable, since they involve the fundamental problem of the public health upon which rests the happiness, prosperity and the very security of the nation. They involve complicated problems that must be solved and their solution will require mature deliberation and dispassionate as well as sober thought. After a long period of lethargy the medical profession is now aroused to the importance of taking an active interest in these questions; in the final solution of which it is earnestly to be hoped that our profession will take a leading part. Certain it is that if their satisfactory solution is not directed by the medical profession from within, some plan, however unwelcome and distasteful it may prove, will ultimately be forced upon the medical profession from without. Nevertheless, as vital as these issues are, the American College of Physicians hardly

provides the proper forum wherein to debate these moot questions. We are essentially a scientific body dedicated to the advancement of clinical medicine; we represent a group of physicians primarily interested in internal medicine. We are in no sense a cross section of the medical profession of this country. As individuals we are entitled to and should hold definite views on all matters involving the welfare of medicine and the community. As members of our National, County and State societies, we can be afforded ample opportunity to take an active part in moulding both lay and medical opinion on these social and economic questions. In our capacity as Fellows of the American College of Physicians it would seem best for us to see to it that this organization adheres purely to the scientific and educational purposes for which it was created. Let us not dissipate our energy, time and resources in costly investigations of and futile debates, which too often become acrimonious, upon subjects which, however important, do not fall properly within the scope of our activities. This is especially true when there exists a great national medical society which, by reason of its almost universal membership, equipment and organization is the one body best able to deal with these problems and to safeguard and readjust the interests of the physicians and the rights of the public.

Although admittedly, as an organization, we are not properly constituted to deal with the varied aspects of medical economics, there is no escaping the fact that as a group of scientifically trained men we have a real interest in the future development and progress of medicine. It is generally recognized that in medicine, as in virtually every other business and professional activity, marked changes have taken place. In the case of medicine, at least, some of these changes seem to have created situations that are not wholly satisfactory either to the profession or the public. Therefore, it seems timely and not out of keeping with the purposes of this College to review some of the factors that have been responsible for these changes and to consider how medicine may advance in the future in order to correct some of the difficulties that have arisen.

If we look back but a couple of generations we find that the practice of medicine was not surrounded by the difficulties and complexities that beset it today. At that period with few exceptions doctors were general practitioners, few specialists existed and even the outstanding surgeons of the day were not above or averse to the duties of general practice. The family doctor of former days has been so often extolled and his virtues and accomplishments have been so thoroughly praised that it is far from my intention to add to these richly deserved eulogies. Suffice it to point out that the general practitioner of the past was more than a physician, he was a socially minded individual who was an important factor in his community and was regarded with confidence and respect. His word was undisputed in all matters pertaining to health and disease. What he may have lacked in scientific training was more than offset by his understanding of and his keen personal interest in his patients and their problems.

In short, he furnished his fellow beings a medical service that was so generally available and so satisfactory that there was apparently neither the occasion nor the opportunity for the vexing problems involved in medical economics to arise.

Gradually, as the exact sciences were more and more applied to medicine, far reaching changes began to take place and what might be termed the modern era in medicine began. About the end of the last century, with the development of bacteriology, experimental physiology and pharmacology, biochemistry and the other medical sciences, medicine as an art began to decline and the science of medicine came into the ascendency. With this trend medical teaching was altered, medical courses were lengthened, classes were restricted in size, premedical requirements were increased, scientists began to replace practitioners as teachers and medical students became imbued with the spirit of research and impressed by the importance of the science of medicine. Who can deny the inestimable value of this changed attitude to the progress of scientific medicine. As the result of all this most of the advances upon which modern medical practice is founded took place. In the last fifty years greater progress has been made in all fields of medicine than occurred during the preceding two thousand. But this era of scientific achievement has not tended to develop any widespread interest among medical students in general practice. On the contrary, it has created in many of them an ambition to pursue the more academic and scientific aspects of medicine to the exclusion of practice, while not a few who have gone into clinical medicine have made haste to enter special fields and have exhibited little enthusiasm for the hardships and inconveniences of the general practitioner.

The outcome of this modern trend in medical thought has been that while medicine, established upon a firm scientific foundation, has advanced to an unbelievable degree, the art of medicine has suffered.

The general practitioner, finding it increasingly difficult to keep pace with the rapidly succeeding changes that have been taking place in medical practice, has been gradually superseded either by out and out specialists or by a group of clinicians who by reason of their ultrascientific training have come to look upon patients more as interesting clinical material than as individuals seeking aid for illnesses that are quite as often dependent upon mal-adjustments in their domestic and social environment as upon objective pathological changes and which require for their correction a broad minded, sympathetic viewpoint on the part of a medical advisor. The public has become conscious of this fact. The intelligent layman, fully alive to the incalculable blessings that medical progress has bestowed upon him, is equally aware that as medicine has advanced it has become more impersonal and more specialized. He realizes that a medical examination today is apt to become a costly and formidable procedure devoid of much of the personal interest and understanding in his individual problems that was so conspicuous in the days when the general practitioner held sway. Although

medicine has changed, the psychology of patients has not. For the most part, they still manifest a desire for personal service much the same as they did in the times of our forefathers, in spite of the advances that have taken place in medicine.

One important result of all this has been that the public, finding that broadly trained, socially minded doctors were too often unavailable, has gradually drifted away from the general practitioner and turned more and more to specialists and special groups. Where once a single physician cared for a patient and helped solve his problems now many are needed, all regarding the patient from some special angle, none being willing to consider him as a whole. As a consequence, as the prestige of the general practitioner has diminished the cost of medical care has increased. The passing of the general practitioner and the rise of specialism has beyond peradventure been an important factor in the much deplored increased cost of medical service.

Those who are concerned in medical education and the many economic problems that now confront us have gradually become aware of the necessity of altering in some way the training of doctors so that there may be available to the rank and file of the people of this country that to which they are justly entitled, a group of physicians who in a modern way can fill the gap created by the passing of the general practitioner of a former generation.

The pendulum of medical education which moved so far toward the purely scientific side is gradually swinging back. Medical schools everywhere show an encouraging tendency to select as their students not only those who show aptitude for scientific pursuits but those who have the preliminary education, social background and personality to develop into efficient practitioners of broad vision and high ideals actuated by an impelling desire to be of service.

To that end, the training of these men, either before or during their medical school days, should not be limited so strictly to biological and medical subjects; it should include the fundamentals of psychology, sociology and economics so that those who go forth into practice may be socially minded, public spirited citizens capable of taking a leading part in the varied activities of their community and of directing popular thought in all matters pertaining to the health and welfare of the people.

It is generally conceded that less than 5 per cent of medical students are qualified to go into the purely academic or research fields of the medical sciences. Dr. Roger I. Lee has recently shown that 85 per cent of medical practice can be successfully carried out by the family practitioner leaving but 15 per cent that requires the services of a trained specialist. From which it may be deduced that not over 10 or 15 per cent of medical graduates are justified in spending the time and money necessary to equip them as specialists, when the majority of any class are best adapted to general practice and should be trained with that in mind.

The " family doctor " of old is gone forever, but his counterpart must

be developed in the form of a physician possessed of an adequate cultural background, scientifically trained in medicine, thoroughly aware of his personal obligations to his patients and capable not only of treating sickness but also of teaching people how to keep well.

As the result of educational campaigns and propaganda we of the medical profession have created in the public a health consciousness that has made it thoroughly alive to the importance of preventing disease as well as curing it. Today the people expect something more of their doctor than mere care during illness, they require someone competent to advise and direct them in all matters pertaining to their health. In short, the general practitioner of the future must be a "health adviser" as well as a physician. With the control of the great epidemic diseases and other advances in preventive medicine the span of life has been steadily increased, with the result that where once the acute infections played a dominant rôle as a destructive factor now the degenerative diseases incident to advancing years and the wear and tear of life have become the most important causes of disabling illness. Consequently, the "man in the street" who is well aware of these changed conditions, is now chiefly concerned in how to escape cancer, how to avoid becoming a diabetic, how to maintain his kidney function, and how to prevent premature occlusion of his coronary or cerebral circulation and other similar questions. It is upon such pertinent health problems as these that he wants and will in time demand sound medical advice and periodic physical examinations. To meet this need the family health adviser of tomorrow must be alive to the requirements of preventive medicine as applied to the individual. He must be prepared to fill satisfactorily the deficiencies along these lines that unfortunately have existed in the past.

So complex and important have the various methods of diagnosis become that it will never be possible for any individual to become proficient in all branches. Therefore, specialists will always be necessary and, as medicine advances, complicated technical procedures will always be required. In order, however, to have all the studies that may be necessary for any given patient properly correlated and evaluated, there should be some one responsible individual capable of acting as a coördinator. This again is obviously the function of the properly trained modern family doctor. In the future, therefore, a definite move should be made to place the general practitioners in a central position among their professional colleagues.

When a new school of medical practitioners shall have been developed and when such practitioners have firmly reëstablished themselves in the minds of the people as their proper health advisers, another important step looking toward protection of the public will take place. As people have sought less and less the guidance of competent general physicians they have acquired more and more the habit of self medication and have fallen victim to the high pressure salesmanship of the drug manufacturers, chain stores, proprietary medicine vendors and a host of other commercialized forms of

advice relative to all varieties of human ills. Fostered by radio broadcasting, popular magazine articles, quasi-scientific lectures and literature and other forms of insidious and alluring advertising, this evil has grown to an enormous extent. It is unnecessary to dwell upon the obvious dangers to health that are brought about by this unintelligent attitude on the part of a thoroughly exploited public. All this has been and is being constantly and admirably done by our national medical society that spares no effort to protect our people. Repeated investigations have shown that each year the American public not only jeopardize themselves but bear an unwarranted economic burden in the vast sums of money which they expend on proprietary remedies and self medication. When this tendency shall have been checked another enormous reduction in the cost of medical care will have been affected. In bringing this about there is no one in such an advantageous position as the modern family physician—an added argument in favor of reëducating the people to look upon such physicians as their legitimate and reliable guides and mentors in all matters pertaining to their well-being.

The members of this College, interested as they must be in the improvement of medical education and the advance of clinical medicine, can do much to further the development of the general practitioner of the future who shall combine the functions of "health adviser" with that of director and coördinator of the medical activities of the people. If in the future, men who embody the qualifications referred to can become the guiding figures in the medical life of our communities, the needs of the public will be adequately cared for and many of the most debated problems of medical economics will be automatically solved.

The modernizing of the family doctor with its attendant curbing of specialization and the inevitable lowering of the cost of medical care, will go a long way toward regaining the confidence of the public in the medical profession. The doctor will be returned to that position of respect, trust and affection which he should occupy in the hearts of the people and, like his predecessors, he will again become an outstanding figure and leader in the affairs of his community and the progress of this nation.

A turning point has come in American medicine. We stand at the crossroads eagerly searching for the guide who can extricate us from the by-ways of uncertainty and point out the highway of progress along which medicine of the future should advance.

The time is at hand when we must look to the more effective control of specialization in medicine, a movement in which the American College of Physicians is bound to play a leading part. Adverse criticism has been directed against the lack of proper regulation of specialization. Control in the sharply differentiated fields of medical practice, such as eye, ear, nose, throat and other specialties, offers little difficulty. The problem becomes more complicated, however, when we attempt to apply it to the broad field

of internal medicine. The solution for the internist may rest in limiting recognition to the subdivisions of internal medicine, as cardiology, gastroenterology, etc.

Your Board of Regents, cognizant of this development, is already active in setting up educational requirements that will be sufficient to guarantee in the future the ability of all successful candidates for Associateship in this College to qualify as internists.

Although the College has made great strides it is destined to further achievements. This is assured by the enthusiasm, ability and distinction of those in whose hands its future rests.

In conclusion, let me again express to you my sincere thanks and appreciation for the honor which you conferred upon me when you saw fit to elevate me to the presidency of the American College of Physicians.

INHIBITORY HORMONES AND THE PRINCIPLE OF INVERSE RESPONSE *

By J. B. Collip, F.A.C.P., *Montreal, Canada*

It has been a matter of great interest to those working in endocrinology to note in the case of many laboratory animals and also in the case of many patients, that a state of lowered reactivity, of increased resistance or of actual non-responsiveness may gradually become manifested in those that have been treated for a long period with some glandular extract. Likewise, it has been observed that certain previously untreated animals or patients may be non-responsive to injections of a known potent glandular extract. We have only to think of the failure of the parathyroid hormone to affect appreciably the blood serum calcium of the rabbit or of the patient who is resistant to enormous doses of thyroid extract.

In the extensive study that has been made in our laboratory during the past two years upon the thyreotropic hormone of the anterior pituitary, it was proved abundantly that animals treated for some weeks with this hormone extract became non-reactive to it. Moreover, it was shown that the injection of the blood serum of such non-reactive animals into normal animals caused these latter also to become non-reactive to administered potent thyreotropic extracts. The production of a serum inhibitory to the thyreotropic hormone therefore became a possibility. Extending our study, it was found that such an inhibitory principle could be demonstrated in the blood of the rat, rabbit, dog, goat and horse after treatment for six weeks or longer with adequate amounts of the thyreotropic extract.

Further evidence both of a direct and an indirect character has been obtained which would tend to show that inhibitory substances for various hormones may appear in the blood of animals treated for long periods with different hormone extracts. Thus hypophysectomized rats have become non-responsive to the purified growth hormone (Q extract) in about 40 days. Rats which have been treated with the ovary stimulating placental hormone for long periods, and in which the ovaries have become non-responsive, still respond to the maturity factor contained in anterior pituitary. Likewise, rats rendered non-responsive to the maturity factor of anterior pituitary still respond to placental hormone.

The serum of animals treated for many weeks with the placental hormone has been shown to inhibit the effect of placental extract in the immature female test object.

The serum of a horse treated for three months with the pituitary growth hormone has been shown to antagonize the effect of growth hormone on the hypophysectomized rat.

* Read at the Chicago meeting of the American College of Physicians, April 17, 1934.
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We have obtained most positive evidence of the presence in the serum of horses treated with certain pituitary extracts of substances inhibitory to the ketogenic effect of anterior pituitary extracts.

It is not my purpose in this communication to discuss the details of the experimental evidence which has been obtained to support the theory that inhibitory hormones are produced as a response on the part of the organism to the introduction of excessive amounts of various hormones. I wish rather to enlarge upon the theory itself.

The production of serum inhibitory to a specific hormone may be viewed in one of two ways. Either the administered hormone extract is acting as an antigen and the inhibitory substance which can be detected in the blood serum of the treated animal is an antibody, or else the inhibitory substance represents a normal constituent of the blood which under normal conditions is balanced, as it were, against the respective hormone in such a manner as to be masked itself. We prefer this latter view, that the inhibitory substance which is found in the blood of animals after prolonged treatment with some hormone extract is a normal constituent of blood. The response of the organism to chronic injections of hormone would consist then in the increased production of the respective inhibitory principle. This theory may be extended further and one may suppose that for each hormone, or at least for many hormones, there exists an opposite, an anti- or inhibitory principle.

We have adopted as a working hypothesis the view that anti-hormones, perhaps better called inhibitory principles, are present in the normal subject. This broad principle is particularly attractive since it may be used to explain such things as the great difference in the responsiveness of different species to hormones as well as minor variations in responsiveness within a species. The theory is not without attraction from the clinical side, since it suggests the possibility that any supposedly hypo-hormone state may just as well be a hyper-inhibitory hormone condition or an imbalance between the hormone and its respective inhibitory principle. If one pictures a hormone and its respective inhibitory principle as a complex and views this complex as a "buffer," then one can introduce a quantitative factor in relation to the level of this complex and one species of animal can be sought in which the "buffer" is normally at a low level and others will be found in which the "buffer" is at a much higher level.

In view of the fact that there are many examples of extreme variation in the response of an individual of one species to administered hormone as compared to the response of an individual of another species similarly treated, I was led to postulate in my Welch lecture [1] a few weeks ago, the theory of inverse response.

The principle of this theory can be illustrated by a specific example:

The pituitary of the guinea pig as compared with that of the rat contains relatively very little of the thyreotropic principle; the thyroid of the guinea pig as compared with that of the rat is relatively inactive; the metabolism

of the guinea pig is at a lower level than that of the rat; the guinea pig is exceedingly sensitive to administered thyreotropic hormone, while the rat is extremely resistant. However, the hypophysectomized rat is exceedingly sensitive to this hormone.

The principle of inverse response of which the above is an excellent example may be stated as follows:

"The responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the individual's own gland."

It is possible to find numerous examples which indicate the very general application of this principle in endocrinology, and as an independent theory it can stand alone. We have been interested, however, in linking the theory of inverse response with the theory of anti-hormones. If one does this then one of the most important implications of the theory is that the level of a hormone is related directly to the level of the corresponding anti- or inhibitory hormone. The demonstration of a hyper-hormone state associated with lowered responsiveness to administered hormone implies the co-existence of a hyper-inhibitory hormone state. One might here draw an analogy between the highly buffered solution which is sluggish in regard to pH change on addition of small amounts of acid or alkali and the hormone resistant animal which is, as it were, well buffered by a high level both of hormone and respective inhibitory principle in its system.

That the effect of a small dose of a hormone will be greater when the existing concentrations of hormone and anti-hormone circulating are small than when they are already large will not be regarded as surprising. In many cases of physiological antagonism between drugs, it is known that the *ratio* between the concentrations of the two antagonists determines the physiological effect, whatever the actual amounts; this has been shown for the interaction of atropine and pilocarpine on salivary secretion,[2] of atropine and acetyl choline on the frog ventricle,[3, 4] of adrenalin and ergotamine on the rabbit uterus,[5] and elsewhere. The *ratio* will obviously be more disturbed by a given *amount* of hormone when the quantities of hormone and anti-hormone present are initially small.

Clinical Applications

The clear-cut demonstration of the production of inhibitory substances in the serum of animals for certain hormones with which the experimental animals have been treated should provide occasion for the serious consideration of those effects of a similar nature which may be produced in patients injected with certain glandular extracts over a long period of time. One sees, for instance, the possibility of the clinician in his endeavor to correct a hypoglandular state actually adding to the gravity of the condition by causing an overproduction of inhibitory principle as a result of too persistent treatment.

While the results of these recent investigations in the laboratory suggest that many dangers may attend the clinical use of glandular extracts, nevertheless they point the way to new applications. If the general principles established by the experimental work are applicable to the human subject, then the possibility must be considered of producing inhibitory hormones in an active way in the system of the patient, or of raising the level of these in a passive way by the use of active extracts of inhibitory sera, the latter produced from horses injected over long periods with adequate amounts of the purified hormones.

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LYMPHOSARCOMA AND HODGKIN'S DISEASE: BIOLOGIC CHARACTERISTICS *

By Solomon Ginsburg, M.D., *New York, N. Y.*

For more than half a century after Hodgkin [1] first described the disease that now bears his name, no sharp line of demarcation was drawn between lymphosarcoma and Hodgkin's disease. Indeed, the two names were considered synonymous by the overwhelming majority of competent investigators of this baffling problem.[2]

In 1893 Kundrat of Vienna recorded a study of 50 cases of lymphosarcoma in which the following tissues and organs were involved: lymph glands, skin, subcutaneous tissues, muscles, breasts, bones, dura, tongue, palate, pharynx, tonsils, larynx, trachea, bronchi, lungs, pleura, thyroid, thymus, pericardium, vena cava, esophagus, stomach, duodenum, jejunum, ileum, cecum, rectum, peritoneum, mesentery, and omentum.

Based principally upon a gross anatomic study of these 50 cases and 100 allied cases, Kundrat [3] sought sharply to differentiate lymphosarcoma from Hodgkin's disease on the following grounds:

Lymphosarcoma	*Hodgkin's Disease*
1. Invades the capsule of lymph glands.	1. Does not invade the capsule of lymph glands.
2. Invades and infiltrates neighboring tissues.	2. Does not invade or infiltrate neighboring tissues.
3. Obliterates normal structure of the lymph glands.	3. Does not obliterate normal structures of the glands.
4. Extension regional, from one group of lymph glands to another or from one lymphoid area to another. Metastases by way of the blood stream are absent or very rare.	4. A systemic disease from the outset like leukemia.
5. Infiltration of hollow viscera by direct extension from involved lymph glands or involved lymphatic channels.	5. Involvement of viscera through blood or lymph channels by the unknown agent of the disease.
6. Invasion of hollow viscera causes dilatation of lumen, never constriction.	6. Involvement of hollow viscera causes constriction of lumen.
7. Rarely invades bone.	7. Frequently invades bone.
8. Invasion of liver and spleen nodular.	8. Invasion of liver and spleen diffuse.
9. Persons between the ages of 25 to 55 most frequently affected.	9. Younger individuals more frequently affected.
10. Male sex twice as frequently affected as females.	10. Female sex more frequently affected.
11. Tuberculosis of the lungs rarely present.	11. Tuberculosis of the lungs frequently present.

The histological description of lymphosarcoma given by Kundrat was limited to the following single paragraph: "As to the histological structure, I have nothing new to add. Lymphosarcomas are characterized by their

* Received for publication April 4, 1934.

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reticular stroma and embedded lymphoid cells. It must be emphasized that the lymphosarcomatous tissue does not resemble normal reticular lymphoid tissue. The typical or normal tissue is replaced by atypical stroma with a variable amount of fibrosis and hypertrophy and hyperplasia of cells which deviate from the normal type."

A careful analysis of this histological description probably explains the reason why Kundrat failed sharply to differentiate lymphosarcoma from Hodgkin's disease on the basis of microscopic structure as he did on gross anatomic considerations. A comprehensive survey of the literature until the time of Kundrat's publication fails to reveal in the great majority of outstanding studies on lymphosarcoma and Hodgkin's disease any distinctive microscopic features by means of which these two diseases could be sharply differentiated from one another.

A definite microscopic differentiation of lymphosarcoma from Hodgkin's disease, which occasionally was met with in the literature, was first strongly emphasized shortly after Kundrat's publication by Paltauf [2] of Vienna, and within the next few years it reached its finished form in the writings of Carl Sternberg [4] of Vienna and of Dorothy Reed [5] of Baltimore.

Based upon a careful microscopic study of 15 cases clinically diagnosed pseudoleukemia or Hodgkin's disease, Sternberg formulated the following differential diagnostic points between lymphosarcoma and Hodgkin's disease.

Lymphosarcoma	*Hodgkin's Disease*
1. Invades capsule of lymph gland.	1. Does not invade capsule of lymph gland.
2. Invades neighboring tissues.	2. Does not invade neighboring tissues.
3. Abundance of atypical lymphoid cells. No endothelial hyperplasia.	3. Abundance of large endothelioid cells with an admixture of lymphoid and plasma cells.
4. Characteristic uninuclear and multinuclear giant cells absent.	4. Characteristic uninuclear and multinuclear giant cells always present.
5. Absence of giant cells and endothelioid cells in the blood and lymph sinuses.	5. Presence of large number of giant cells and endothelioid cells in the blood and lymph sinuses.
6. Absence of Langhans giant cells.	6. Presence of Langhans giant cells.
7. Absence of caseation necrosis.	7. Frequent presence of caseation necrosis.
8. Tubercle bacilli absent.	8. Tubercle bacilli frequently present.

The differential diagnostic features between lymphosarcoma and Hodgkin's disease drawn by the Viennese pathologists gained immediate acceptance in the scientific medical world. The only phase that met with prompt dissent by a number of competent students of this problem was the rôle of the tubercle bacillus in the etiology of Hodgkin's disease. One of the foremost among these dissenters was Dorothy Reed of Baltimore, whose classical description of Hodgkin's disease has received widespread and well-merited recognition in the English speaking world.

Accepting in the main Sternberg's histologic description of Hodgkin's disease and stressing in addition the frequent presence of eosinophiles, Reed correctly pointed out that Langhans giant cells, caseation necrosis and tubercle bacilli are an associated condition in Hodgkin's disease and not a part of the disease. In a series of eight cases clinically diagnosed Hodgkin's

disease at The Johns Hopkins Hospital a careful histological study during life revealed the characteristic pathological histology of Hodgkin's disease. In none of the specimens studied were the histological features of tuberculosis revealed or tubercle bacilli detected. In one of the cases that came to autopsy an associated miliary tuberculosis was discovered, which was interpreted as a terminal infection.

Based upon her own studies and a review of the literature, Reed agreed with the Viennese pathologists that Hodgkin's disease was purely an inflammatory granulomatous process but entirely rejected the tubercle bacillus as the underlying cause of the disease for the following reasons:

Tuberculosis	*Hodgkin's Disease*
1. Necrosis and caseation are the rule.	1. Necrosis and caseation are rare unless secondary infection occurs.
2. Invades and breaks through the capsule of the gland.	2. Does not invade and break through the capsule of the gland.
3. Shows miliary tubercles or general inflammatory changes with typical caseation, Langhans giant cells and tubercle bacilli.	3. Shows typical non-tuberculous histology unless complicated by tuberculosis as a secondary phenomenon.

When tuberculosis occurs in Hodgkin's disease, Reed concluded, it is always a distinct pathological condition and may be present either as (*a*) a concomitant condition in different organs, (*b*) an associated condition in the same organs or tissues affected by Hodgkin's disease, or (*c*) a terminal condition in the course of the disease.

Thirty-one years have now elapsed since Reed's classical description of Hodgkin's disease. During these years a voluminous literature has sprung up dealing with the various phases of lymphosarcoma and Hodgkin's disease. With few exceptions, the overwhelming majority of investigators have embraced the viewpoint of the Viennese pathologists that a sharp line of demarcation exists between lymphosarcoma and Hodgkin's disease. Lymphosarcoma is regarded as a frankly neoplastic disease while Hodgkin's disease is looked upon as a purely inflammatory granulomatous process—a lymphogranuloma.

Among the first clear dissenting voices sharply disagreeing with the views of the majority were those of Benda [6] and Chiari and Yamasaki.[7] In a small series of cases of typical Hodgkin's disease observed by them, careful morphological studies revealed invasion of the capsule of the glands and of the veins. The chief biologic characteristics which distinguish a malignant neoplasm from a benign growth, namely, invasive growth into the neighboring tissues and vascular channels, were found by them to be present not only in lymphosarcoma but also in Hodgkin's disease. The most important differential points which Kundrat had stressed between lymphosarcoma and Hodgkin's disease were thus proved to be untenable. Nor did their studies corroborate the views of Sternberg that Hodgkin's disease is merely an atypical form of tuberculosis masquerading in the guise of pseudoleukèmia. The tubercle bacillus was entirely excluded as a causative

factor in the group of cases of Hodgkin's disease studied by them histologically and bacteriologically.

In 1906 Gibbons [8] of San Francisco published a careful morphological study of nine cases of classical Hodgkin's disease. These strikingly brought to view the incorrectness of Kundrat, Paltauf and Sternberg's differential criteria between lymphosarcoma and Hodgkin's disease. In Gibbons' cases the capsule of the gland was invaded, the neighboring tissues were invaded and infiltrated, the normal structure of the gland was obliterated, the mode of extension was regional and metastatic-hematogenous, the invasion of liver and spleen was definitely nodular, eight of the nine patients were adults and all of them males. In no case was tuberculosis found as an associated condition.

Gibbons was especially impressed by the invasion of blood vessels and the hematogenous mode of dissemination of the proliferating cells. Contrary to the belief which still prevails today among many eminent pathologists that Hodgkin's disease develops only in areas of preëxisting lymphoid tissue by the invasion of the unknown infectious agent of the disease, Gibbons noted that the specific lesions in the viscera seem to originate in the vicinity of blood vessels. In one of the cases " in which the lung was affected, the metastases showed plainly that they were not alone developments of preëxisting lymphoid tissue in the organ, but progressed as true malignant metastases by pushing the tumor structure already formed into adjacent tissues, destroying them, and occupying their places, while large nodular metastases occurred in the lower lobe removed from the invading part of the tumor and not in the vicinity of the bronchi—that is in a situation where no lymphoid tissue exists normally."

Having been thus impressed by the gross anatomic malignant characteristics of Hodgkin's disease, which fully paralleled those of lymphosarcoma, Gibbons carefully reviewed the morphological-histological reasons that have induced many pathologists then—as well as now—to declare Hodgkin's disease a non-neoplastic inflammatory granulomatous infectious disease. These reasons dogmatically given then as now are: In neoplastic growth it is only one type of cell which shows the proliferative growth, while in granulomatous proliferation many cells participate in the process. In lymphosarcoma the growth is composed entirely of atypical lymphocytes, hence it is a true neoplasm, while in Hodgkin's disease there is a polymorphous proliferation of endothelioid cells, lymphocytes, fibroblasts, eosinophiles, giant cells, polynuclear cells, plasma cells and mast cells.

Gibbons' conclusion was that morphologically also there is no fundamental distinction between Hodgkin's disease and lymphosarcoma. Histologically, he found that the pathological tissue in Hodgkin's disease is composed of a proliferation of cells of the germinal centers of the gland, the endothelium lining the sinuses, the reticulum cells of the connective tissue, capsule and blood vessels. The proliferation may go on simultaneously from the three sources or one may outstrip the others. *If it goes on with*

the same tempo in all the three tissues the morphological picture is that of classical Hodgkin's disease; if one cell type outstrips the others we have more in the foreground the sarcomatous nature of the process. The correctness of this viewpoint is attested by the transition stages of affected glands in which even the staunch supporters of the inflammatory granulomatous nature of Hodgkin's disease find it difficult or impossible to differentiate it from sarcoma and have therefore suggested a Hodgkin's type of sarcoma.[9] Clinically, biologically, and morphologically, Gibbons concluded, Hodgkin's disease and lymphosarcoma are not sharply demarcated diseases but merely variations of the same malignant neoplastic process, namely, lymphosarcomatosis.

One year later, in 1907, Coley[10] stated: "My own conclusion, based upon a study of upwards of 600 cases of sarcoma, 76 originating in the lymph glands of the neck, is that Hodgkin's disease is merely a variety of sarcoma, maintaining as a rule a fairly definite clinical and pathological type, but yet, in many cases, shading off into other types that correspond most closely with the ordinary types of round cell sarcoma. If the malignant nature of the disease becomes generally accepted, as I believe it undoubtedly will, it will be hard to find a better name for the disease than lymphosarcoma or lymphosarcomatosis."

In 1908 further studies by Coley[11] and Dietrich[12] stressed the local invasive character of Hodgkin's disease and its frequent invasion of veins, hence favoring hematogenous dissemination. Nevertheless, the sharp line of demarcation between lymphosarcoma and Hodgkin's disease was stoutly maintained in the standard textbooks and monographs dealing with Hodgkin's disease; and, even in the two outstanding comprehensive studies on Hodgkin's disease by Fabian[13] and Ziegler[14] published in 1911, in spite of a wealth of evidence in favor of the close clinical, biological, and morphological relationship between Hodgkin's disease and lymphosarcoma, their fundamental difference was strongly upheld. This nearly universal viewpoint was disturbed in 1911 by only one dissenting case report by the veteran pathologist Chiari,[15] who recorded the autopsy findings in a case clinically and microscopically diagnosed Hodgkin's disease. The findings showed compression of the esophagus, invasion of lungs and pericardium, and discrete nodules in the spleen. Microscopically, the normal architecture of the lymph glands was gone. The capsule was invaded, the fat and bronchi were infiltrated, and the veins and arteries were definitely invaded. A search for tubercle bacilli and Fraenkel and Much[16] organisms proved negative.

In 1913 Oliver[17] published a study of 22 cases of lymphosarcoma, 11 cases of Hodgkin's disease and 13 cases of endothelioma of lymph nodes. His conclusions are: Hodgkin's disease must be classed with lymphosarcoma and endothelioma of lymph glands as a neoplastic process for the following reasons:

1. The similarity, and in certain cases the identity, of the histologic process.

2. The early and constant invasion of the capsule and veins.

3. The ultimate formation of true metastases, partly at least through the blood stream.

In none of the cases of Hodgkin's disease studied by Oliver was there any histological evidence of the presence of tuberculosis or of the Fraenkel and Much organism.

In 1914 it appeared as though at last the true nature of Hodgkin's disease as a mere variation of lymphosarcoma was gaining recognition among the official teachers of pathologic histology. For, that year marked the publication of "The Principles of Pathologic Histology" by Dr. Frank Mallory,[18] an outstanding student of morphological histology, who classed Hodgkin's disease among the frankly neoplastic diseases as a lymphoblastoma, a mere variation of lymphosarcoma. Indeed, he overreached himself when he designated Hodgkin's disease as scirrhous lymphoblastoma, for certainly Hodgkin's disease during its early evolution has a phase as highly cellular as lymphosarcoma. On the other hand, lymphosarcoma, as stressed by Kundrat [3] in his original paper on lymphosarcomatosis, presents during the course of its evolution a scirrhous stage, phase, or variety as in Hodgkin's disease.

Was it overemphasis of the late degenerative or regressive phase or stage of Hodgkin's disease and the slighting of the early highly cellular polymorphous phase of the disease which accounts for Mallory's failure to make sufficient impression upon the profession? Or, was it the apparently ultra-radical view—a view already suggested by Banti [19] in 1903—which would embrace in one group Hodgkin's disease, lymphosarcoma and lymphatic leukemia—which made Mallory's classification unacceptable to the majority of pathologists who are strong adherents of static morphological histology? Whatever the explanation is, the fact remains that Mallory's views found very limited acceptance among pathologists outside the Harvard group.

In 1915 one of the early students of our problem, Dr. William B. Coley,[20] published a comprehensive monograph on "Primary Neoplasms of the Lymphatic Glands Including Hodgkin's Disease." His vast experience and further studies since his first publications on the disease had thoroughly impressed upon him the common nature of lymphosarcoma and Hodgkin's disease. "In one of my cases," he states, "a tumor of the axillary glands was pronounced in the original report, lymphosarcoma, and the same pathologist described it two years later as an endothelioma. Other specimens were pronounced round-celled sarcoma by one pathologist and Hodgkin's disease by another. This is common observation." The same year Bloomfield [21] reviewed the bacteriological evidence produced by Fraenkel and Much,[16] de Negri and Mieremet,[22] Bunting and Yates,[23] and others pur-

porting to show that Hodgkin's disease is an infectious disease caused by diphtheroid organisms. His conclusions were:

1. Organisms can frequently be cultivated intra vitam from diseased as well as from apparently normal glands.

2. There is a higher proportion of successful cultures from definitely diseased glands than from those apparently in a normal condition.

3. None of the 29 strains isolated in the author's series of cases could be shown to be the cause of specific disease.

4. Pleomorphic diphtheroid organisms were isolated not only in a few cases of Hodgkin's disease but also in lymphosarcoma, carcinoma, arthritis and other conditions.

5. Injections of diphtheroid organisms into a monkey failed to produce any definite lesions.

6. Autogenous vaccine therapy given in two cases of Hodgkin's disease and in three cases of infectious arthritis failed to produce any results.

One year later, 1916, Ghon and Roman [24] published a comprehensive study on lymphosarcoma based upon an extensive review of the literature and a thorough histological study of 31 cases. They draw a sharp distinction between Hodgkin's disease, which they consider as a lymphogranuloma, and lymphosarcomatosis, which they regard as a frankly neoplastic disease. They state that clinically and gross-anatomically the two diseases cannot always be differentiated. One wonders, however, how can such differentiation always be made even on the basis of histological morphology in the light of their verified observation: "In lymphosarcoma we find fairly represented all the cellular elements of lymphadenoid tissue: lymphoblasts, lymphocytes, macrophages, plasma cells, and even giant cells."

Perhaps even more important than this observation of the presence of polymorphism of cells in lymphosarcoma as in Hodgkin's disease was their observation of the frequent invasion of blood vessels by the lymphosarcomatous growths and their tendency to hematogenous metastases, as in Hodgkin's disease. Kundrat's original claim that hematogenous metastases in lymphosarcoma are absent or very rare and that extension of the disease is from one group of lymph nodes to another or from one lymphoid area to another—a belief still widely held today by many clinicians and pathologists—was entirely disproved by Ghon and Roman's thorough and careful histological observations. A detailed study of the mode of dissemination of lymphosarcoma in 27 out of their 31 cases revealed:

1. Direct extension and metastases to regional lymph nodes in six cases.

2. Direct extension and metastases to regional and distant lymph nodes in four cases.

3. Lymphogenous and possibly hematogenous metastases in five cases.

4. Local lymphogenous and hematogenous metastases in 12 cases.

Two years later Warfield and Kristjanson [25] reported a case which on first admission to hospital gave the distinctive pathologic picture of lympho-

sarcoma. Upon readmission the blood picture was that of acute lymphatic leukemia, while glands removed from the axilla just before death showed a picture indistinguishable from typical Hodgkin's disease.

In 1917 Cunningham [26] again reviewed the status of diphtheroids with special reference to Hodgkin's disease and produced proof that the diphtheroid organism in a series of cases of Hodgkin's disease was a mere laboratory contamination and could not be obtained in typical cases of Hodgkin's disease when careful bacteriological methods were used to prevent contamination.

In 1921 Mueller [27] published a study of 16 cases of Hodgkin's disease. In two of the cases the disease exhibited "a change in the histological structure from typical lymphosarcoma to round-celled sarcoma or vice versa. In one of the two cases the disease exhibited malignant neoplastic properties with invasion of lungs, aortic wall, and spinal canal." From a morphologic-histological point of view," Mueller concluded, "the opinion seems justified that lymphosarcoma and round-celled sarcoma of the lymph-nodes are only different expressions of the same process."

In 1925 another one of Kundrat's differential diagnostic dogmas between lymphosarcoma and Hodgkin's disease was completely disproved by Liu [28] of Pekin, China. In a study of 12 cases of lymphosarcoma of the small intestine from the pathological department of The Johns Hopkins Hospital, Baltimore, Liu found stenosis of the gut in 10 of the cases. Kundrat's original observation of the presence of dilatation in lymphosarcomatous tumors of hollow viscera—which led him to the hasty generalization that invasion of hollow viscera by lymphosarcoma causes dilatation of lumen, never constriction—was thus proved untenable, and once again the danger of generalizing from a comparatively small number of cases was emphasized.

One of the most instructive cases of Hodgkin's disease showing its close relationship, if not identity, with lymphosarcoma was published by McCartney [29] in 1928. A woman of 52 developed progressive loss of weight, pallor and dyspnea, followed one year later by enlargement of the cervical lymph glands. A biopsy of one of these glands was reported small round-celled sarcoma. Several months later, in 1927, nodes removed from the neck and axilla were reported lymphatic leukemia. The patient died in March 1928. Autopsy revealed invasion of lymph glands, skin, lungs, liver, and kidneys by nodular growths.

Microscopic examination showed: "In one lymph node four distinct histologic types are present. In some areas one sees the typical picture of Hodgkin's disease with Dorothy Reed type of cell. In other areas the appearance is that of lymphatic leukemia. In many places there are numerous spaces lined by an endothelial type of cell, giving an appearance simulating closely but not quite duplicating that of primary endothelioma of lymph nodes. Finally certain areas show a large type of cell with marked

evidence of active growth, with numerous mitotic figures and a small amount of reticulum, an appearance commonly called lymphosarcoma. Scattered through the node are microscopic areas of necrosis and marked fibrosis." The involved visceral organs showed similar histological pictures.

The same year, 1928, Coley [30] reported a new series of 58 cases of lymphosarcoma and 39 cases of Hodgkin's disease. He reiterates: "For many years I have held that these two conditions, which are usually regarded as quite different and distinct, are actually quite closely allied etiologically, and bear such a close resemblance to one another that in some instances it is impossible to differentiate them either clinically or histologically."

Further recent studies entirely in agreement with the view that Hodgkin's disease and lymphosarcoma are merely variations of the same malignant neoplastic process were recorded by Letulle, Trémolières and Moussoir,[31] Callender, [32] Warthin,[33] Levin,[34] Wellbrock and Lougherty,[35] and others.

My own observations and studies during the past 13 years, based upon more than 100 cases of Hodgkin's disease and lymphosarcoma, are entirely in agreement with the viewpoint that biologically, clinically, and morphologically they are merely variations of the same disease. To justify this viewpoint, in the course of our study, abundant detailed evidence will be submitted, of which the following two case reports will serve as introductory illustrative examples.

Case I

Mrs. V. G., aged 54, was admitted to the Montefiore Hospital on September 13, 1929, complaining of pain in the right shoulder, a lump in the right axilla, progressive weakness, and loss of weight. Duration of symptoms, seven months.

In February 1929, without any apparent predisposing or exciting causes, she developed pain in the right shoulder. A few weeks later she discovered a painless lump in the right axilla. Prompt medical consultation resulted in a diagnosis of tumor of the right axillary lymph glands and operation was advised. A resection of the tumor was done on April 28, 1929, by a prominent New York surgeon, who found the mass "composed of glands of various sizes. Some were quite hard and felt like carcinoma, others were much softer and had the appearance of sarcoma." The pathologist's report was typical Hodgkin's disease.

One week after the operation the patient developed an acute chest condition which was diagnosed as pneumonia. The respiratory symptoms subsided within a few weeks but her general health showed progressive deterioration. She became very asthenic and partly bed-ridden.

On admission to the Montefiore Hospital on September 13, 1929, she looked pale and emaciated. The mouth showed a few remaining carious teeth and no other abnormality. There were many stony hard and matted together lymph nodes in both cervical regions. There was a scar in the right axilla and no recurrence of any tumor mass. The lungs showed slight dullness at apices and bases. The heart showed no abnormalities. The liver was palpable about 5 cm. below the costal margin. The spleen and kidneys were not palpable. There was a median ventral hernia. The rectal and vaginal examinations were negative.

Radiographic examination of the chest on September 20, 1929, revealed normal lungs and mediastinum and moderate left ventricular enlargement.

Blood examination showed hemoglobin 90 per cent; white blood cells 10,000; polynuclear leukocytes 78 per cent; lymphocytes 20 per cent; eosinophiles 2 per cent. The blood Wassermann was negative. Urinalysis was essentially negative.

Course under Roentgen Therapy. Following deep roentgen display to the cervical lymph nodes the masses decreased in size but the patient's general condition gradually grew worse. Reëxamination on January 12, 1930, found her complaining of profound weakness and a completely bed-ridden state, dryness of the throat, cough and expectoration, profuse night sweats, pain in the right upper posterior chest, pain in both arms and in the lumbosacral spine. She looked paler than on admission. The following superficial lymph glands were found to be enlarged: right pre-auricular, left cervical, left axillary, right epitrochlear, and left inguinal. The right breast was enlarged and markedly edematous. The skin over it had a typical pig-skin appearance. The lungs and heart did not show any gross abnormality. The abdomen failed to reveal any tumor masses. The spleen was not palpable. The liver was felt 5 cm. below the costal margin. The lower extremities showed slight edema.

On February 23, 1930, a hard, immovable, circumscribed, tender mass measuring 5 by 5 by 3 cm. was noted over the upper sternal region and contiguous chest wall. The mass felt bony-hard in consistency and seemed to be fused with the ribs and sternum. At this time a radiographic examination of the chest revealed an area of consolidation in the right lower lobe. It also showed a slight thickening of the periosteum along the anterior surface of the first portion of the sternum. There was a partial collapse of the body of the seventh dorsal vertebra to about half its size.

The predominant clinical symptoms were toxic and respiratory. She ran a remittent febrile course with temperatures to 103°. A blood count, done on March 18, 1930, showed 3,600,000 red blood cells, 75 per cent hemoglobin and 8,600 white blood cells. The polynuclear leukocytes were 86 per cent; lymphocytes 8 per cent; monos 4 per cent; eosinophiles 1 per cent; and basophiles 1 per cent.

Cautious deep roentgen-ray therapy was applied to the chest lesions with little effect upon the course and development of her illness. She steadily went down hill and died from toxemia and respiratory embarrassment on September 27, 1930.

Necropsy revealed: (1) Hodgkin's disease involving the cervical, mediastinal, periaortic, retroperitoneal, mesenteric, peri-pancreatic and iliac lymph nodes; the thyroid, right breast, both lungs, right bronchial tree, spleen, pancreas, stomach, jejunum, cervix, vagina, bladder and vertebral bone marrow.

2. Bilateral hydronephrosis.

3. Chronic purulent cholecystitis, cholangitis and cholelithiasis with stones in the hepatic duct and in the papilla of Vater.

4. Ulceration of the neck of the gall-bladder.

5. Extreme fatty metamorphosis of the liver.

Detailed Study of the Hodgkin's Lesions. Skin and Breast: Above the right breast and extending into the axilla is a 16 cm. old scar. The right breast is about twice the size of the left. The skin is thickened and wrinkled and shows two fairly punched-out ulcerations. There is considerable edema of the right arm. Over the skin of the chest the infiltration is rather hemorrhagic in character. On section, the right breast shows a plum-sized mass of exceptional firmness, homogenous, grayish in appearance, rather gristly in texture, from which strands of similar tissue are seen to extend crab-like through the adipose tissue and into the underlying tissue. The pectoral muscles are almost completely absorbed and the fascia above the thorax is markedly infiltrated by this firm, gray tissue. Microscopically the lesion presents the typical picture of Hodgkin's disease. The wall of one of the veins and its vasa vasorum show invasion (figures 1 and 2).

Bones: Four contiguous lumbar vertebrae examined reveal diffuse replacement of red marrow by a yellowish, homogeneous, firm tissue.

Neck Organs: The cervical lymph nodes are enlarged and on section show a similar firm, homogeneous tissue. There is a small, circumscribed, whitish-gray nodule in the right lobe of the thyroid. Microscopically the nodule, apparently a lymph node,

FIG. 1 (Case I). Diffuse invasion and infiltration of Hodgkin's disease in the wall of a breast vein. Suspicion of invasion of vasa vasorum.

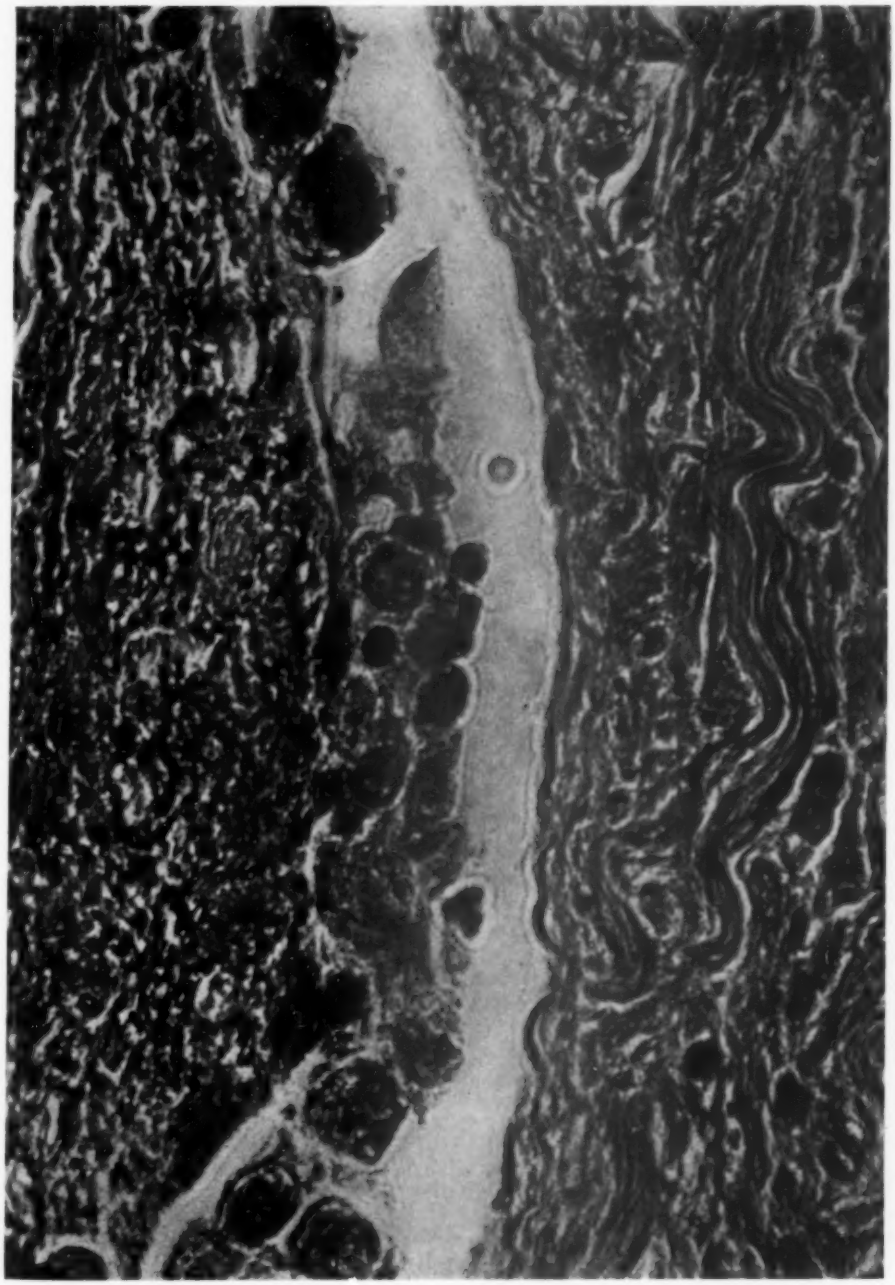

FIG. 2. Invasion of vasa vasorum by Hodgkin's reticulum and giant cells.

entirely replaced by Hodgkin's tissue, is seen to infiltrate the capsule and invade the thyroid (figure 3).

Trachea and Bronchi: The mucosa of the trachea is slightly injected. Beginning just above the bifurcation there is a marked alteration of the mucosa of the bronchus

FIG. 3 (Case I). Invasion of thyroid by Hodgkin's disease.

which is considerably thickened, very irregular and apparently replaced by a similar very firm, homogeneous, grayish tissue. The change extends into the smaller ramifications of the bronchi to both upper and lower lobes. Tracheo-bronchial lymph nodes are enlarged and very firm. On section they are markedly degenerated but are definitely invaded by a similar tissue.

Lungs: The right lung feels heavy and there is a peculiar sensation on palpation due to scattered areas of almost wooden consistency throughout the entire lung. Posteriorly and over the anterior surface of the upper lobe there is complete obliteration of the pleural cavity. The remaining surface of the lung has a mottled emphysematous and congested appearance. The lung is very pale. Occasionally one sees beneath the pleura a circumscribed, very small raised nodule composed of a

homogeneous grayish tissue. On section there is an astounding picture. The upper lobe is almost entirely replaced by exceedingly firm, raised, pigmented, homogeneous, grayish tissue which is very sharply defined from the pale and somewhat edematous normal lung. These nodules, varying in size from an orange to a plum, constitute about three-quarters of the upper lobe. The lower lobe is fairly well aerated, pale in color. Scattered throughout are small circumscribed nodules of a similar, very firm, grayish, slightly pigmented tissue. The parietal pericardium is firmly adherent to the mesial surface of the right lung.

Microscopical Examination: Many of the alveoli are filled with fibrinous material and serum. In the interstitial tissue and extending into the alveoli are typical Hodgkin's tissue, Dorothy Reed giant cells, occasional lymphocytes and areas of fibrosis and necrosis.

The mediastinal lymph nodes are markedly enlarged. Microscopical examination shows typical Hodgkin's.

Heart: Extreme fibrosis. Marked calcification of the coronaries.

Abdomen: The peritoneal cavity is free from fluid. The mesentery is atrophic and contains numerous enlarged and discrete lymph nodes which on section contain a very firm grayish tissue from which no juice can be scraped. Some of these nodules show a considerable amount of pseudo-mucin.

Spleen: Slightly enlarged. Weighs 210 gm. Measures 12 by 8 by 5 cm. The capsule is smooth, slightly wrinkled and reddish-gray in appearance. Notches are well preserved. On section the pulp has a fleshy, rather homogeneous appearance, and yields little on scraping. Trabeculations are quite marked. Near one blood vessel is an almost wedge-shaped area made up of very firm grayish tissue. At the lower pole there is replacement of the pulp over an area the size of a cherry by a very firm, glistening, grayish tissue. Microscopic examination reveals large areas of necrosis and hemorrhage with areas of fibrotic Hodgkin's tissue. The uninvolved portion of the spleen shows atrophy of pulp tissue with very small follicles.

Stomach and Jejunum: On the anterior wall of the stomach in the fundus, are two circumscribed, dime-sized ulcerations of the mucosa with fairly thickened walls. Numerous enlarged nodes are present along the attachment of the mesentery to the peritoneal surfaces of the small and large intestines. In the mid-portion of the jejunum there is an ulceration of the mucosa about 4 by 1.5 cm. whose long diameter is perpendicular to the direction of the intestines. The edges of the ulceration are very firm and are raised. On the serosal surface are several small collections of firm, grayish tissue which are in relation with a very large node in the mesentery near by. Microscopically the mucosa and submucosa are infiltrated with typical Hodgkin's tissue.

Gall-Bladder and Liver: Free from any neoplastic tissue on gross and microscopical examination.

Pancreas: A small area at the head of the pancreas containing compressed but relatively normal tissue is all that remains of the normal pancreas. The remainder, including the body and tail and a portion of the head, is replaced by a very firm, homogeneous, rather gristly tissue in which are a few yellowish areas (figure 4). This infiltration of the pancreas causes a threefold increase in the size of the involved portion. Numerous lymph nodes in this region at the head of the pancreas and along the greater and lesser curvature of the stomach are replaced by similar tissue.

Suprarenals: Normal in size and shape and free from tumor tissue.

Kidneys: Free from tumor. Both pelves and ureters are slightly dilated. The terminal thirds of both ureters are in close relation to and compressed by a chain of enlarged lymph nodes extending from the bifurcation of the aorta along the iliacs to the femoral region.

Iliac Vessels: Are firmly ensheathed in a large group of lymph nodes.

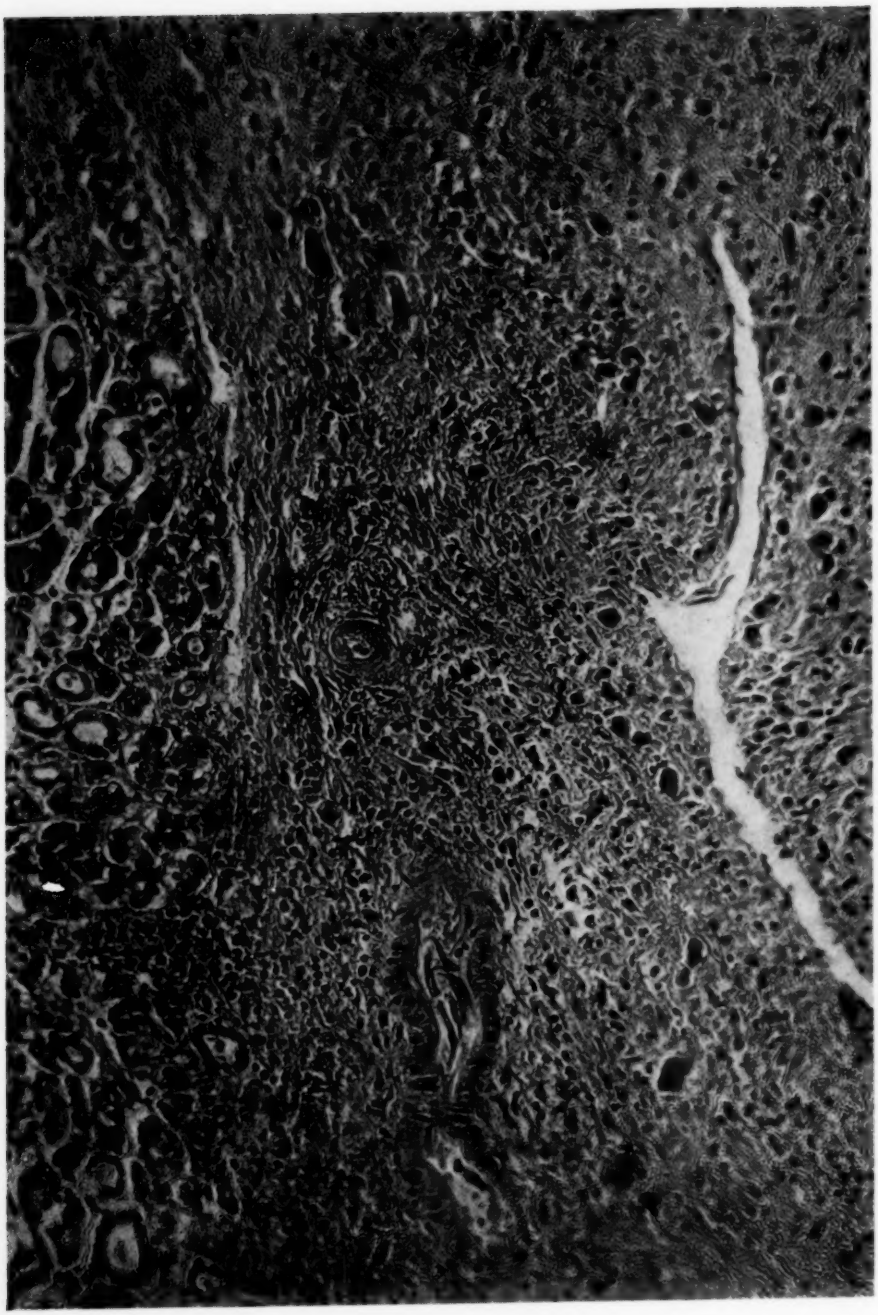

FIG. 4 (Case I). Invasion of pancreas by Hodgkin's disease.

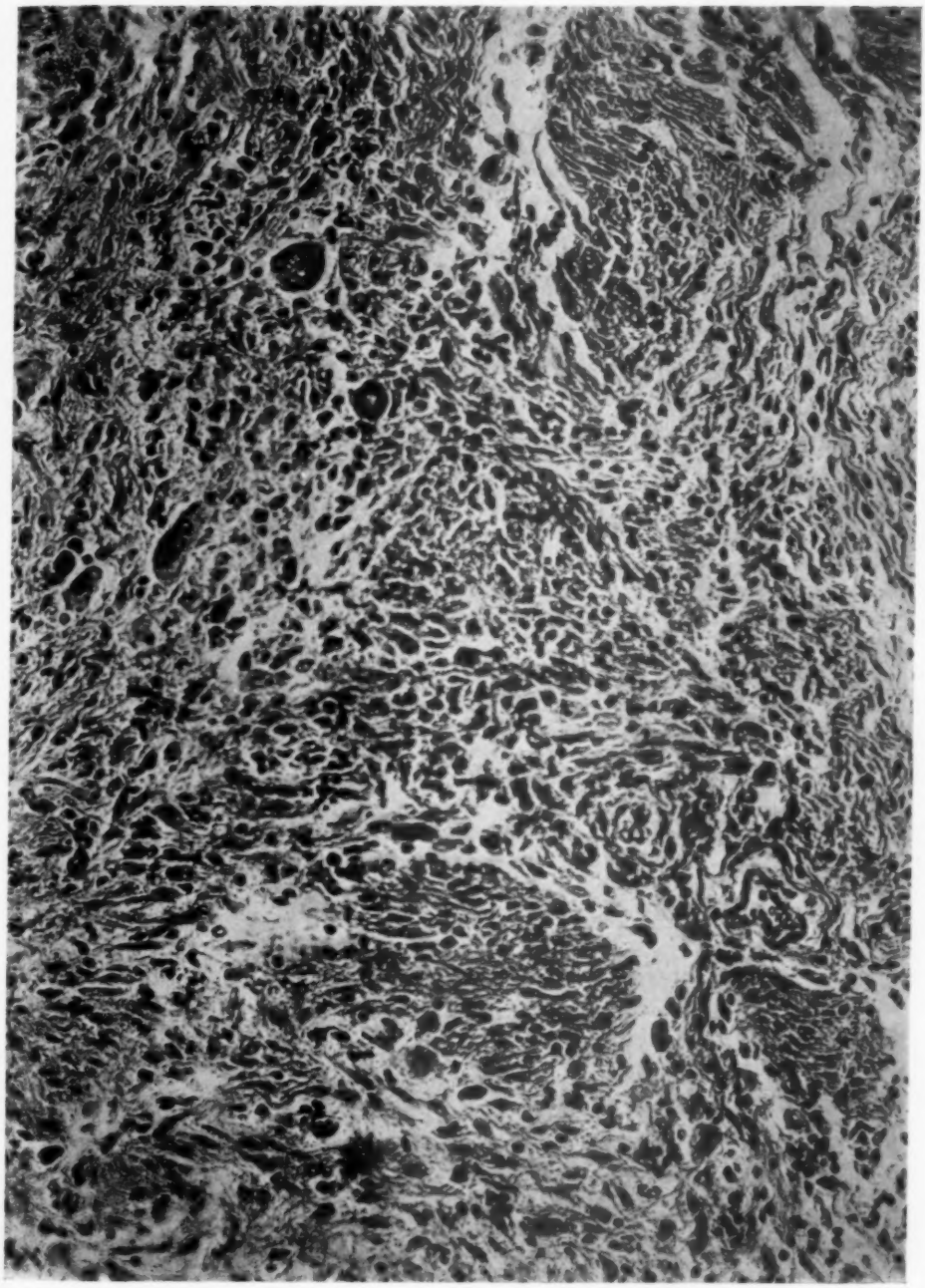

FIG. 5 (Case I). Invasion of uterus by Hodgkin's disease.

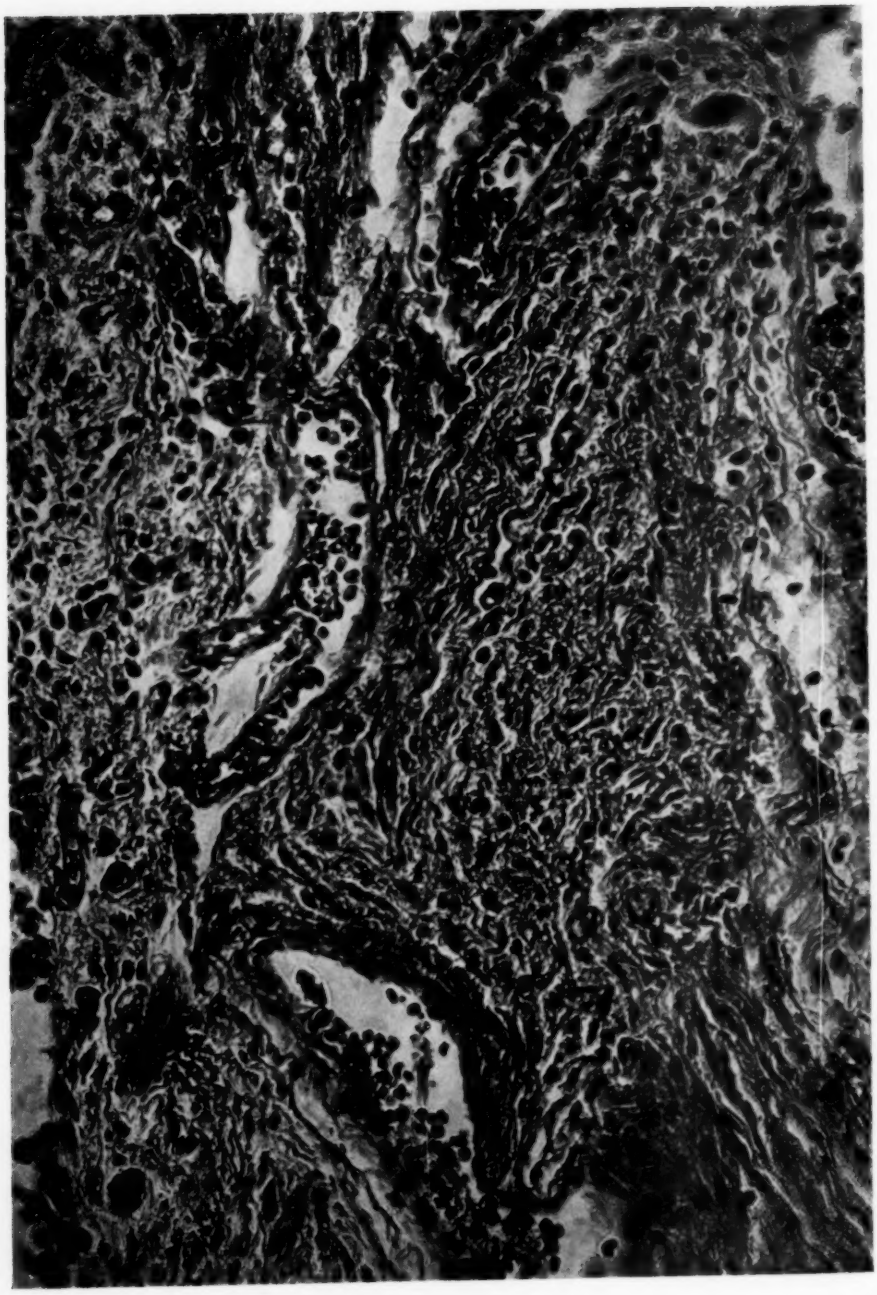

FIG. 6 (Case I). Invasion of bladder by Hodgkin's disease.

Ovaries: Fallopian tubes and rectum are free from tumor.

Uterus: The upper right fundal portion of the uterus is replaced by a homogeneous yellowish-gray appearing tissue which is confined entirely to the muscular coat (figure 5). The cervix is markedly enlarged and on section contains similar tissue.

Vagina: The upper portion of the vagina shows numerous serpiginous ulcerations, and submucosal thickenings caused by growth of similar very firm tissue.

Bladder: Grossly no evidence of tumor growth. Microscopically the wall of the bladder is infiltrated by Hodgkin's tissue (figure 6).

Case II

Mrs. M. H., aged 61, journalist, was admitted to the Hospital on February 21, 1924.

Chief Complaints: Pain in upper abdomen, left lower posterior chest, left lumbar and lower sacral regions, paraplegia, parasthesia of lower extremities, tumor mass over hip, marked weakness and loss in weight. Duration of symptoms, 14 months.

Present Illness. On January 1, 1923, without any apparent predisposing or exciting causes, while stooping forward to lace her shoes she was seized with a violent twisting pain in the left upper abdomen, recurring several times during the day and lasting each time a few minutes. The next day she consulted a local physician who diagnosed visceroptosis and advised the wearing of an abdominal belt. The belt was promptly donned and gradual subsidence of pain in the abdomen followed. Shortly thereafter she experienced a dull aching pain in the left lower lateral chest. She immediately consulted another local physician who discovered an enlarged spleen and had her blood examined. Internal medication was prescribed with gradual relief of the pain in the chest. In February she began to have drawing and twisting deep-seated pain in the upper mid-abdomen sharply localized and non-radiating. The pain was constant and severe but was not accompanied by any other local or constitutional symptoms. In May she consulted another local physician who diagnosed myalgia and myositis and prescribed a liniment and internal medication. In June she began to have very severe pain in the lower part of the spine aggravated on motion. She was forced to spend most of the time in bed to obtain partial relief from pain.

In July her daughter, while giving her a rub-down with alcohol for the sore lower spine, discovered a mass the size of a hen's egg over the right hip. The mass was neither painful nor tender and according to the patient's observation had apparently not undergone any change in size until admission to Montefiore Hospital some six months later.

In August she was taken to a large hospital in New York where her spine was radiographed and pronounced negative. The presence of the lump over the right hip apparently elicited no comment or attention and she was discharged with a diagnosis of lumbago.

Gradually the pain in the lower spine increased in severity, disability became more marked and she became almost completely bed-ridden.

In November she consulted a gynecologist for cystocele which she herself had noticed a year before and which she now suspected as the possible cause of her severe and disabling backache. The presence of cystocele was confirmed and at her own request a pessary was inserted. The gynecologist, however, did not feel quite convinced that the cystocele was the sole cause of the underlying complaints and advised orthopedic consultation. This was promptly agreed to. She was examined by an experienced orthopedist who ordered a brace for supposed spondylitis. Unfortunately, however, neither brace nor pessary produced any relief from the severe backache and within a few days after their application she developed prickling and numbness in the soles of both feet gradually extending upward to the hypogastrium and associated with weakness of both lower extremities.

In December the pessary was removed but the paraplegia became more pronounced and she was unable to sit up in bed.

In January 1924, she was admitted to a hospital in New York where her case was diagnosed as postero-lateral sclerosis of the lower lumbar cord possibly due to tumor. The presence of a tumor over the right hip and invasion of the lungs by neoplasm were also noted but their exact interrelationship was not understood. The patient was given a series of intramuscular injections without the slightest benefit and on February 21, 1924, nearly 14 months after the onset of her first complaints, she was admitted to the neurological service of Dr. Philip S. Goodhart at the Montefiore Hospital.

Examination revealed an old pale-looking and emaciated woman presenting no cachexia, dyspnea or cyanosis. The skull and scalp were negative. The teeth were almost all gone; only a few badly carious ones remained. The tongue was heavily coated and tremulous and the left half was atrophic. The tonsils were small and buried behind the pillars. The pharynx was free from any neoplastic disease. The neck showed no enlargement of lymph nodes. The thyroid gland was not palpable.

Chest and Lungs: Diminished vocal fremitus and dullness from the top of the right scapula to the base. A few slightly enlarged lymph nodes were palpable in the left axilla, none in the right.

Heart: Negative.

Abdomen: Distended, tympanitic. On deep palpation a diffuse doughy mass can be felt along the midline. The liver is palpable 4 cm. below the costal margin, the surface is smooth, the edge sharp. The upper level of liver dullness extends to the fifth intercostal space. The spleen is palpable 1 cm. below the costal margin. The iliac, inguinal and femoral lymph nodes are greatly enlarged, discrete, non-tender, varying in size from ½ to 2 to 3 cm. Over the left gluteal region a mass the size of a hen's egg, soft, non-tender and freely movable, is present.

Rectal and Vaginal Examination: Negative.

Neurological examination reveals involvement of the twelfth cranial nerve evidenced by slight fibrillary tremor affecting the whole tongue and atrophy of its left half. There is definite paraplegia. A sensory belt of hyperesthesia begins about two inches above and ends about two inches below the umbilicus. Below this belt there is hypesthesia. Very little motion is possible in the lower extremities. The patient can just lift her knee off the bed but cannot maintain it in that position. There is a bilateral Babinski and markedly exaggerated knee jerks.

Laboratory Data: Radiographic examination of the chest shows a dense homogeneous shadow extending from the right apex to the base. Blood examination: moderate secondary anemia. White blood cells 11,200; polynuclears 74 per cent; small lymphocytes 9 per cent; large lymphocytes 6 per cent; mononuclears 6 per cent; mast cells 2 per cent; eosinophiles 2 per cent. Urine analysis practically negative. Biopsy of lymph node shows large reticulum cell lymphosarcoma.

Course under Roentgen Therapy: Following deep roentgen therapy to the lower spine and chest there was slight recession in symptoms. The further clinical course of the disease was mainly characterized by further generalization of the neoplastic process, progressive wasting, persistent toxemia and terminal pneumonia superimposed upon the neoplastic lung involvement.

Necropsy revealed generalized lymphosarcoma with involvement of mediastinal, retroperitoneal, iliac and inguinal lymph glands, thyroid, sternum, pleura, lungs, heart, peritoneum, small intestines, adrenals, liver and kidney.

Detailed Autopsy Report: The body is that of an elderly, slenderly built, markedly emaciated female, 150 cm. long.

Scalp, brain, pituitary and pineal negative.

Eyes, ears and nose negative.

Mouth: Mucous membranes pale.

Teeth: Many missing, remainder well kept.

Tongue: Negative.

Tonsils: Small, pitted, scarred.

Larynx and Trachea: Normal.

Neck: Negative except for a few shotty glands on both sides along the lateral borders of the sterno-mastoid.

Thyroid: Both lobes slightly larger than average, the right hard though smooth. There is an elongated nodule of apparently normal thyroid on the right side of the midline separate and distinct from the right thyroid lobe which measures 1.5 by 0.5 by 0.3 cm. On section, the greater portion of the right lobe with the exception of the upper pole is replaced by smooth grayish white tissue in the center of which is a small area of calcification. The left lobe contains an ill defined nodule 1.5 cm. in diameter in its upper pole; the remainder of the lobe is apparently normal and colloid containing. Microscopic examination shows isolation and replacement of thyroid follicles by tumor throughout.

Parathyroids: Normal.

Upper Extremities: Negative.

Chest: Breasts atrophic. Slightly to the left of the midline in the region of the third and fourth ribs is a bulgy, firm tumor mass about 7 cm. in diameter, over which the skin is freely movable. The mass is seen to infiltrate the elevated intercostal muscles and the medial portions of the pectoral muscles. The removal of the sternum and costal cartilages is accomplished with difficulty because of extensive tumor involvement of the mediastinum and the anterior surface of the pericardial sac.

Pericardial Sac: There is a wide layer of tumor tissue externally which binds the pericardial sac to the medial surface of both lungs. On opening the pericardial sac, both the visceral and parietal surfaces are covered with a shaggy fibrinous layer and in the parietal pericardium are numerous flattened grayish white tumor nodules, discrete and confluent, measuring up to 2 cm. in diameter and 5 cm. thick.

Heart: Weighs approximately 200 gm. The entire visceral pericardium is covered with shaggy fibrinous exudate. On section the heart muscle is decidedly brown and injected. No abnormalities are found in the endocardium or valves. *Microscopic:* Muscle fibers are thinned out, the vessels slightly thickened. An organizing fibrinous layer is found on the epicardial surface. In the edematous epicardium is a small tumor area.

Right Pleural Cavity: Is completely obliterated in its upper two-thirds; in its lower third it is filled with a hemorrhagic fluid containing large fibrin masses. The parietal and visceral pleura all over is markedly thickened and in the region of the diaphragm measures 5 mm.

Right Lung: The two upper lobes are air-containing throughout. The lower lobe is markedly collapsed, atelectatic. On section, both upper lobes are markedly edematous and slightly congested, the lower lobe collapsed and dry. The tumor tissue in the visceral pleura measures up to 7 mm. in thickness along the diaphragmatic and visceral borders. The bronchi are slightly dilated. The larger arteries are slightly but distinctly thickened throughout. The root glands are enlarged, grayish white, firm.

Left Pleural Cavity: Contains about 700 c.c. of clear straw colored fluid and a few dense fibrous adhesions at the apex of the upper lobe and over the posterior surfaces of both lobes. There are numerous small tumor nodules on the parietal pleura.

Left Lung: Both lobes are fairly well collapsed. A few fibrous tags are present on the parietal surfaces. There is a healed scarred area at the apex of the upper lobe. Scattered throughout the visceral pleura of both lobes are flattened nodules

up to 1 cm. in diameter and 3 mm. thick. On section, both lobes are moderately congested and edematous. The bronchi are dilated, the vessels normal. The root glands are markedly enlarged and at the hilum they surround the larger bronchi and appear underneath the mucous membrane. *Microscopic:* Extensive replacement and diffuse tumor infiltration of lungs with areas of necrosis and fibrosis.

Abdomen: Spleen small and free from tumor.

Liver: Weight 880 gm. Small, soft. Capsule thin. On the inferior surface are numerous small nodules up to 1 cm. in diameter, 3 mm. thick. On section, tissue greasy brown; lobulations fairly regular; numerous tumor nodules up to 5 mm. in diameter are seen and a single large nodule 2 cm. in diameter. Microscopic examination reveals invasion of veins by tumor cells.

Esophagus and Stomach: Negative for tumor.

Duodenum: There is an elevated nodule 7 mm. in diameter and 2 mm. thick, immediately anterior to the ampulla. The remainder of the duodenum is negative.

Jejunum and Ileum: At irregular intervals are numerous, slightly flattened, nodular, grayish white and injected tumor nodules in the mucous membrane, measuring from 3 to 7 mm. in diameter and 2 to 4 mm. thick. These nodules are numerous in the jejunum and do not infiltrate the muscle layers.

Pancreas: Free from tumor.

Appendix: Coiled up in a mass of adhesions though on section the lumen is patent throughout.

Cecum: Except for a nodule of tumor tissue on its peritoneal surface in the region of the adhesions described, no abnormalities are seen. Microscopically tumor tissue infiltrates the muscle layers and the peritoneal coverings of the cecum and appendix.

Colon: No abnormalities.

Suprarenals: The right suprarenal weighs 5.5 gm. and is of average size and consistency. On section, the cortical tissue is narrow and fatty, and the medulla is softened. The left weighs approximately the same and is for the most part adherent to the tumor tissue on its posterior surface. On section, the cortical tissue is fatty, the medulla is prominent, and there is a small tumor nodule 5 mm. in diameter in the medulla.

Kidneys: Each weighs 110 gm. and is of average size and consistency.

Right: Capsule slightly diffusely adherent and in places firmly adherent to large tumor nodules. The nodules appear on the surface as slightly elevated, grayish white nodular areas up to 2 cm. in diameter and slightly umbilicated. The remainder of the surface shows marked superficial pitting. On section, there is slight congestion throughout. The tumor nodules are seen to replace large portions of the cortex and pyramids, but in places the architecture is still retained. The striations are regular and prominent. At the hilum the tumor tissue is seen surrounding but not occluding the larger vessels. Pelvis and ureter negative.

Left: Contains small tumor nodules but is otherwise similar to the right. The large arteries are markedly thickened.

Ovaries, tubes, vagina, and bladder are free from tumor.

Microscopic: The tumor consists of fairly uniformly sized, small polygonal cells with irregular nuclei; the latter are in instances pale staining, and occasionally multilobulated. There are a moderate number of mitotic figures, rarely a syncytial giant cell. In places the cells are small and round, resembling lymphocytes.

Comment

A parallel study of the above two cases reveals the following very instructive facts:

1. Both were females past middle life.

2. In neither case was there any predisposing or exciting cause to explain the etiology of the disease.

3. In neither case was tuberculosis found on postmortem examination.

4. Invasion of the capsule of lymph glands and invasion and infiltration of neighboring tissues occurred in the Hodgkin's case no less than in the lymphosarcomatous case.

5. Obliteration of the structure of glands occurred just as freely in the one as in the other.

6. Extension in the Hodgkin's as well as in the lymphosarcoma case was regionally invasive and metastatic through lymph and blood channels. Invasion of veins and hematogenous mode of systemic dissemination were demonstrated in both.

7. Infiltration of hollow viscera did not differ from metastatic invasion in epithelial cancerous growths.

8. In both cases bone was invaded.

9. The lesions in both were predominantly nodular or diffusely infiltrative in different tissues and organs.

10. Both diseases, although widely generalized, were, on gross and microscopic study limited to about the same number of organs and tissues, as follows:

Lymphosarcoma Case	*Hodgkin's Case*
Lymph glands, thyroid, bone, pleura, lungs, heart, peritoneum, small intestine, cecum, appendix, adrenals, liver, kidney.	Lymph glands, thyroid, skin, bone, breast, lungs, bronchi, spleen, pancreas, stomach, jejunum, uterus, vagina, bladder.

11. Necrosis and hemorrhage occurred in lesions of both types. Though fibrosis was more marked in the case of Hodgkin's disease the clinical course of the disease was not materially altered thereby.

12. Both ran a mild remittent fever.

13. Eosinophilia in the blood was absent in both.

14. Toxemia and cachexia were more marked in the case of lymphosarcoma than in that of Hodgkin's disease.

15. Both died from toxemia and pulmonary involvement without any marked compression of mediastinal structures.

16. The clinical duration of life was 24 months in the lymphosarcoma case as against only 20 months in the Hodgkin's case.

Biologically, therefore, Hodgkin's disease varies in no fundamental characteristic from lymphosarcoma. Whatever variations it may present at times are merely variations that one would expect to find in any disease affecting different individuals under different constitutional and environmental conditions.

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THE ENCEPHALITIS EPIDEMIC IN ST. LOUIS *

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DURING the summer and autumn of 1933, 1097 cases of epidemic encephalitis were reported in St. Louis and in St. Louis County.[1] Study of the disease has revealed that it differs in many important respects from the encephalitis lethargica of von Economo and that it is not definitely identifiable with the Japanese Encephalitis B. Although it has previously attracted little attention, it may not be entirely new in this country. In 1932 cases of a similar condition were seen in the small city of Paris, Illinois, where in a population of 9000, 27 cases were reported.[2, 3]

Due to a most effective organization of the Health Department of St. Louis and to admirable coöperation between local and Federal agencies, unusual opportunities were afforded for study of the entire epidemic.[4] Over 90 per cent of the reported cases were treated in hospitals where clinical records are readily available. The correlation of these data has been placed in the hands of a committee which is representative of the many agencies involved in the work and which will soon publish a comprehensive monograph. Although the report of the committee will furnish an authoritative and detailed analysis of the clinical and laboratory observations, it does not seem inappropriate that a brief outline should be presented before the College of Physicians at this time, more particularly since outbreaks of a similar character and of greater or less severity may possibly occur in other communities during next July, August and September.

The summer of 1933 in St. Louis was unusually hot and dry. June was the hottest ever recorded. After heavy spring rains there was a prolonged drought and in June, July and August the rainfall was the lowest in the history of the city. Conditions of drainage were favorable to the breeding of extraordinary numbers of mosquitoes.

It is now known that a case of encephalitis was seen as early as July 7 and that several isolated cases were observed in St. Louis County during that month. A state of epidemic became dramatically apparent on August 8, when the City Isolation Hospital received from the county 16 cases of an unusual type of encephalitis. Others rapidly followed. Since such an experience was entirely new in this country it is not surprising that much confusion in diagnosis occurred. Because of the severe headaches and high fever, the not infrequent bradycardia and leukopenia, typhoid was often suspected. It is interesting that requests for Widal tests from the health department were 100 per cent higher than in a similar period of the previous year. In some cases the chill of onset led to a suspicion of malaria. Signs of meningeal irritation with increased mononuclear cell count in the spinal

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fluid suggested even to experts the probability of tuberculous meningitis. When from pathological studies encephalitis was demonstrated, it was naturally assumed that the disease was encephalitis lethargica in an atypical form and that it would be followed by the usual distressing residuals. The well justified fear of encephalitis lethargica and its consequences no doubt contributed to the widespread attention given to an epidemic which, although serious, involved only about one in one thousand of the population in a limited area.[1]

Clinical Features

Clinical study of the disease has revealed a striking similarity in the symptoms of individual patients with modifications referable in large part to the intensity of infection, the localization of lesions, to age and previous physical and mental constitution.[5, 6, 7] A typical case of maximum severity may be cited.

A white woman of 53 left her home on the morning of September 6 apparently in good health. While working she was suddenly seized with severe headache and vomiting. She soon became delirious and on the following day was somnolent. On September 9 when she was brought to Isolation Hospital she was stuporous, her temperature was 105°, and her pulse rate was 154. The conjunctivae were injected. There was moderate injection of the naso-pharynx, a marked rigidity of the neck, a gross tremor of the lips and tongue, absent abdominal reflexes, exaggerated deep reflexes, positive bilateral Kernig and extensor response to plantar stroking of both great toes. The white blood cell count was 10,200. The spinal fluid was under increased pressure, gave a positive Pandy test and contained 82.0 mg. per cent of sugar. There were 200 cells per cu. mm. with 90 per cent of lymphocytes. The urine contained albumin, red blood cells, white blood cells and casts. Two days later she died with a temperature of 107.4°.

A milder case and one more representative of the disease as it occurred in children was seen in a colored boy of six. On August 27 he was seized with headache and vomiting followed by drowsiness and pain on bending his neck. Two days later he entered the Isolation Hospital, where examination revealed a temperature of 103°, an injected pharynx, a tremor of the tongue, slight rigidity of the neck, and diminished deep reflexes. There were no pathological toe signs and the abdominal reflexes were present. The white blood cell count was 9400. The urine was normal. The spinal fluid was under moderately increased pressure and contained 130 cells, 91 per cent of which were lymphocytes. The Pandy test was negative. Sugar, as determined by the Benedict method, was present in the fluid. His temperature fell by lysis and in three days was normal. He was discharged on September 21 without symptoms or signs of disease.

An extremely mild case observed by Dr. T. C. Hempelmann may also be cited. This was a 19 year old girl who, although she had had headache, photophobia, a sensation of fever for a period of six days, had not been

confined to bed. At the time of entrance to the hospital she was found to have 107 cells in her spinal fluid. Five days later and on the eleventh day of her disease she felt entirely well and wished to go home.

The purposes of this paper permit no extensive analysis of symptoms. In about half the cases the onset of the disease was sudden, often with a chill or with vomiting, occasionally with convulsions, which were seen in adults as well as in children. In other patients there seemed to be a period of invasion for three or four days with fever, headache, general pains, photophobia and conjunctivitis and slight rigidity of the back and neck. At the end of this prodromal period a sharp rise in temperature was common and the subsequent course was similar to the cases of more abrupt onset.

Although several patients revealed no fever during the period of observation, the usual temperature at the height of the disease was 103 to 104°, in occasional cases rising to 106°. The pulse was usually proportional to the temperature but bradycardia was not infrequent and tachycardia was observed in some of the more severe cases.

Headache, stiff neck, and a positive Kernig sign were relatively constant symptoms. Although diplopia or blurring of vision was noted in many, strabismus, ptosis, and facial weakness were relatively uncommon, occurred early and were usually transient. The abdominal reflexes, which varied greatly with the stage of the disease, were often absent during acute severe illness. The deep reflexes varied too greatly to be of diagnostic importance. Pathological toe signs were not infrequently encountered.

Coarse tremors of the hands and arms often increased by intention and gross tremors of the tongue were seen in many cases. The speech was uncertain and tremulous. Although many patients appeared somnolent or even stuporous, they could usually be aroused sufficiently to answer questions. In a few cases delirium and sleeplessness were prominent features.

The white blood cell count usually ranged from 10,000 to 14,000 with extremes from 2800 to 36,000. During the acute stage the Schilling differential revealed a moderate infectious picture but was not sufficiently characteristic to serve as an aid in diagnosis or prognosis.

The spinal fluid during the acute stage was often under increased pressure. In the majority of instances 100 to 300 cells were recorded but this was subject to considerable variation and in one fluid 1100 cells were found. Lymphocytes usually predominated, although at times polynuclear cells constituted from 30 to 50 per cent of the total. It is important to note that in some cases the fluid withdrawn on the first spinal puncture was normal while a second puncture a day or two later revealed the characteristic increase in cell count. Of diagnostic significance were the sugar determinations which by the Shaffer-Hartmann method varied from 20 to 146 mg. per cent, in the great majority of cases being well above the range seen in tuberculous meningitis.

The urine, often normal, showed in many instances albumin and casts,

but in amounts not greater than those encountered in other acute infections. In a few cases changes indicative of extensive renal damage were found.

A relatively short course was characteristic of the disease. The fever usually remained high from three to five days, and then gradually fell, reaching normal in 7 to 10 days after the onset. A critical drop in temperature, however, was not uncommon. Somnolence or stupor persisted during the febrile course. The cell count in the spinal fluid often remained high after all subjective symptoms had disappeared and in some cases was still elevated three weeks after the onset when the patient was discharged from the hospital.

Prognosis

Among 1059 cases there were 221 deaths, a mortality of almost exactly 20 per cent.[1] The prognosis was not clearly dependent upon the degree of meningeal involvement, the height of the initial temperature or the number of cells in the spinal fluid. The age of the afflicted individual was of the greatest importance, the mortality being less than 5 per cent in patients under 40 and approximately 50 per cent in those over 60. Most of the deaths were attributable in part to complications, by far the most

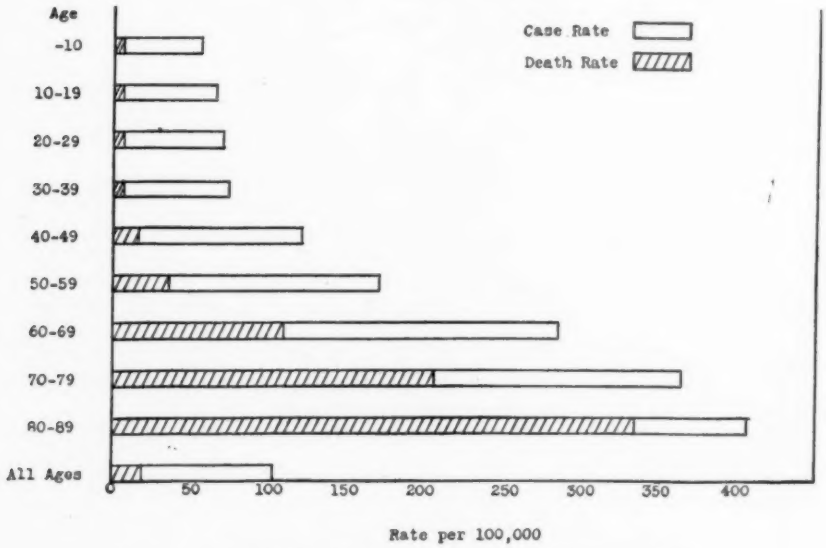

Fig. 1. Incidence and Mortality Rate at Various Ages.
(Data from the St. Louis Health Department.[1])

frequent of which was pneumonia. Previously existing nephritis, hypertension and arteriosclerosis seemed to play an important rôle. Several patients who had not been previously recognized as nephritics died in uremia. Not more than 10 per cent of the deaths could be attributed to uncomplicated encephalitis.

Although serious residual manifestations were uncommon, some degree of disability was apparent in many patients at the time they were discharged from the hospital. In December, approximately three months after the subsidence of the epidemic, an examination was made of 375 of the 447 surviving patients in the City of St. Louis. Of these, 133 revealed no residual symptoms. One patient had remained in a state of delirium. Another was subject to convulsions. Paralyses or localized weakness of muscles were seen in 21. Personality changes such as excitability, melancholy or sullenness were found in 45. Forgetfulness or confusion, usually slight, was not uncommon. Tremor of some degree was still apparent in 72 patients. The most usual complaints were of headache and general pains. Sleeplessness, weakness and fatigue were also frequently mentioned. While this survey has shown that complete recovery occurred after three months in less than half the cases, it is fair to say that most of the changes were slight and that few were disabling. Especially encouraging is the fact that no new symptoms of encephalitis had developed and that there was no single instance of progression of the disease.

Pathology

The pathological lesions, although sufficiently distinctive to establish a diagnosis of encephalitis, did not serve to differentiate sharply the cases of the St. Louis epidemic from those of encephalitis lethargica. Possibly

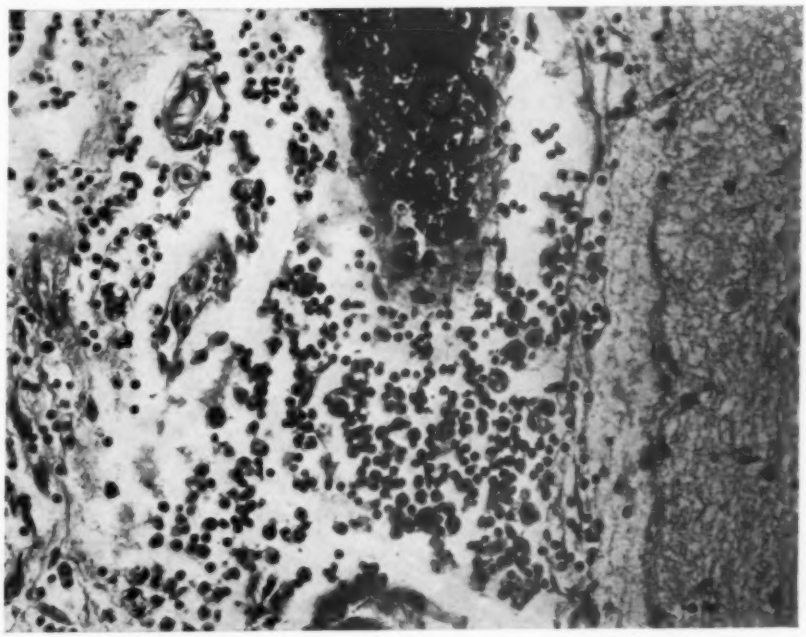

Fig. 2. Section of brain and meninges showing extensive infiltration of the meninges by cells, most of which are lymphocytes.

the most notable difference was the widespread distribution of the lesions in the St. Louis form of the disease. Characteristic changes [8] were found in the meninges and throughout the brain, in the cortex, in the white substance of the hemispheres as well as in the pons and basal ganglia. They were also seen in the spinal cord. To the naked eye the most striking change was the congestion and dilatation of meningeal and intracerebral blood vessels. Capillaries were distended sufficiently to give to many parts of the brain a pinkish discoloration. The diagnosis usually depended upon (1) the intense congestion of blood vessels; (2) the infiltration of round cells about blood vessels, the so-called perivascular cuffing; and (3) the nerve cell degeneration which consisted of swelling, eccentricity of the nucleus and chromatolysis and which was usually accompanied by focal accumulation of round cells. It is of clinical interest that the nuclei of the cranial nerves were not especially involved.

In many of the fatal cases there was a hemorrhagic and edematous type of pneumonia similar to that observed in individuals dying early in the course of acute epidemic influenza. The kidneys were frequently swollen and intensely congested, with cloudy swelling of the cortex and extensive degenerative changes in the convoluted tubules. In several cases intranuclear inclusions, first noted by Dr. Margaret Smith, were demonstrated in the tubular epithelium.

Etiology

The disease has been reproduced by intracerebral inoculation both in monkeys and in mice. While only about 40 per cent of monkeys are susceptible even to large inoculations, white mice may be uniformly infected by material in one-millionth dilution. Brain virus instilled intranasally in mice also has produced the disease. The lesions produced in experimental animals are consistently those observed in human cases. The investigations of Muckenfuss, Armstrong and McCordock,[9] and of Webster and Fite [10] have failed to demonstrate bacteria either in the blood or spinal fluid of patients or in the brains of experimentally infected animals. Webster has shown that the virus is filterable. Thus far 11 strains of virus transmissible to mice have been obtained in four different laboratories.

It has also been shown that the sera of patients recovered from the St. Louis type of encephalitis possess neutralizing antibodies.[10] Diluted virus suspended and incubated with convalescent serum does not kill mice, whereas the same virus mixed with normal serum kills regularly. To a lesser degree antibodies are present in the sera of some of the nurses and doctors who were exposed to the disease but were never ill. Neutralizing properties against the virus have also been shown in the sera of five patients who had recovered from encephalitis in Paris, Illinois, and of two patients from New York who had suffered from encephalitis thought to resemble the St. Louis type.[11]

Fig.

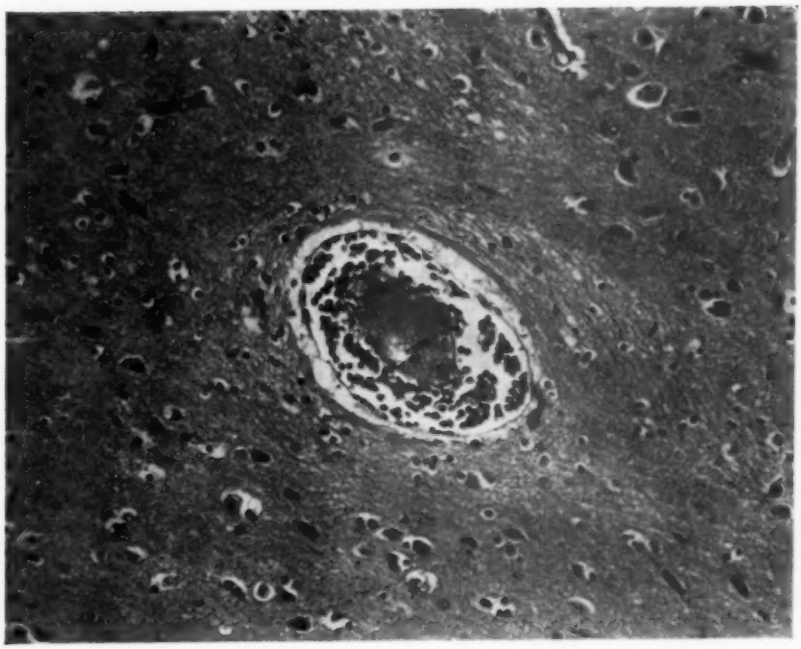

FIG. 3. Section of brain showing perivascular infiltration (cuffing) with lymphocytes.

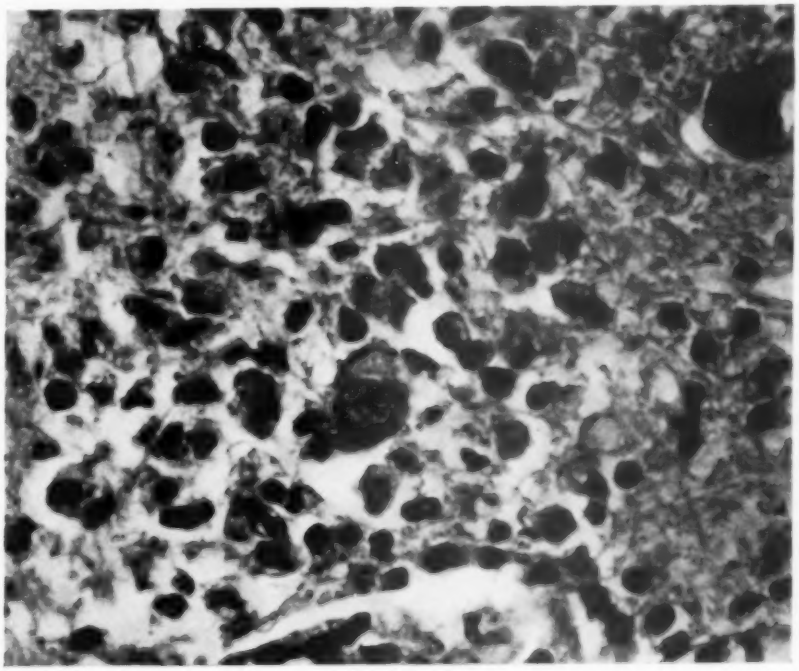

FIG. 4. Higher power showing cellular infiltration about nerve cells. At the upper right there is a degenerative nerve cell in which no nucleus is visible.

The contention [12] that lethargic encephalitis and the St. Louis type of encephalitis are one and the same disease is fraught with many difficulties. The sudden onset, the relatively short course, the prominence and severity of meningeal symptoms, the low incidence of cranial nerve palsies and particularly the rarity of serious residual and progressive lesions are features difficult to reconcile with the clinical picture of encephalitis lethargica. Furthermore, neutralization tests have indicated that those who are suffering from lethargic encephalitis have no neutralization antibodies for the St. Louis virus.[11]

On the other hand, the clinical manifestations of the Japanese Encephalitis B are almost identical with the St. Louis disease. In both there is an acute onset, high fever, meningeal as well as cerebral involvement, a short rapid course with recovery or death in a week or 10 days. In both there is a relatively low incidence of sequelae. The Japanese disease has occurred in the late summer and early fall and has carried a high mortality in older individuals. In the light of this striking similarity of clinical features, it is surprising that the sera of Japanese patients apparently do not neutralize the St. Louis virus.[13]

Summary

The encephalitis which occurred in St. Louis in 1933 was an acute disease of relatively short duration which so far has shown little tendency to serious sequelae. Both its incidence and its mortality were greater in older people. It was caused by a filterable virus to which both monkeys and white mice are susceptible. The sera of patients who have recovered from the disease contain neutralizing antibodies. Both clinically and immunologically the St. Louis epidemic differs from encephalitis lethargica. Although in its epidemiological and clinical manifestations it closely resembles the Japanese Encephalitis B, immunological reactions have indicated that the two diseases are not identical. At present it appears that the St. Louis form of encephalitis has previously escaped general attention and that it is not definitely identifiable with any known condition. The circumstances of the epidemic indicate that it may appear in other communities and presumably in the summer and autumn.

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CHANGES IN THE S–T SEGMENT OF THE ELECTROCARDIOGRAM IN ACUTE RHEUMATIC FEVER*

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Prolongation of the a-v conduction time and alterations of rhythm are the electrocardiographic changes best known to occur in the presence of acute rheumatic fever. A review of the rather scattered literature, together with our own case reports, indicates, however, that S–T (R–T) changes are not uncommon. They deserve much attention because they indicate objectively alterations of the heart musculature.

Case I

The patient was a male, aged 25 years, who was seen first in the hospital February 14, 1933. He gave a history of rheumatic fever at seven years and of chorea at nine years of age. Six weeks previous to examination he had a recurrence of rheumatic infection followed by loss of weight, dyspnea and a left-sided paralysis of short duration. Examination revealed dyspnea, clubbing of the fingers, pallor, enlargement of the spleen and liver, one skin nodule and some glandular enlargement. There were pain and stiffness in several joints. The apex impulse of the heart had its maximum intensity in the anterior axillary line in the sixth intercostal space. A loud diastolic murmur was heard best in the third and fourth left intercostal spaces; and to the right of the sternum was heard a systolic murmur transmitted into the vessels of the neck. There was no evidence of pericarditis. The heart rate was 102 per minute and regular. The pulse was characteristic of the Corrigan type. The blood pressure was 130 systolic and 80 diastolic. The blood count showed 3,860,000 red blood cells, 10 grams of hemoglobin and 16,400 leukocytes. The Wassermann was negative. Roentgen-ray examination showed marked enlargement of the left ventricle and slight enlargement of the left auricle. There were increased pulsations of the left heart contour and aorta, and complete absence of signs of congestive lung failure.

The patient received salicylates and later a vaccine. He improved subjectively and objectively. Six weeks after admission, his red cell count had risen to 4,570,000; his hemoglobin to 13.5 grams and his white blood cells had decreased to 11,100. The pulse rate had dropped to 70. The heart findings remained unchanged. The blood pressure was 150 systolic and 20 diastolic. The patient eventually recovered from his acute rheumatic attack and was discharged from the hospital.

A series of electrocardiograms was taken during the course of this patient's illness. They showed interesting variations in the S–T segment and the T-wave, these variations being dependent apparently upon the stage of activity of the rheumatic infection.

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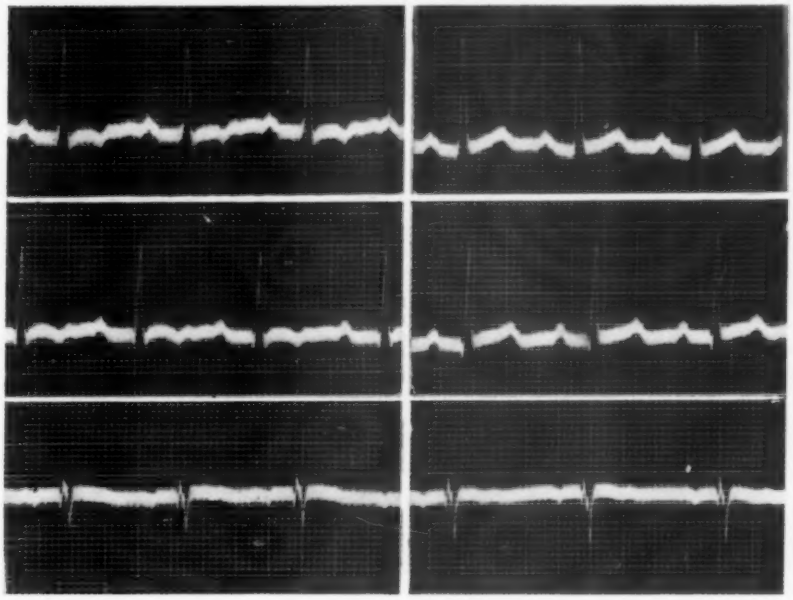

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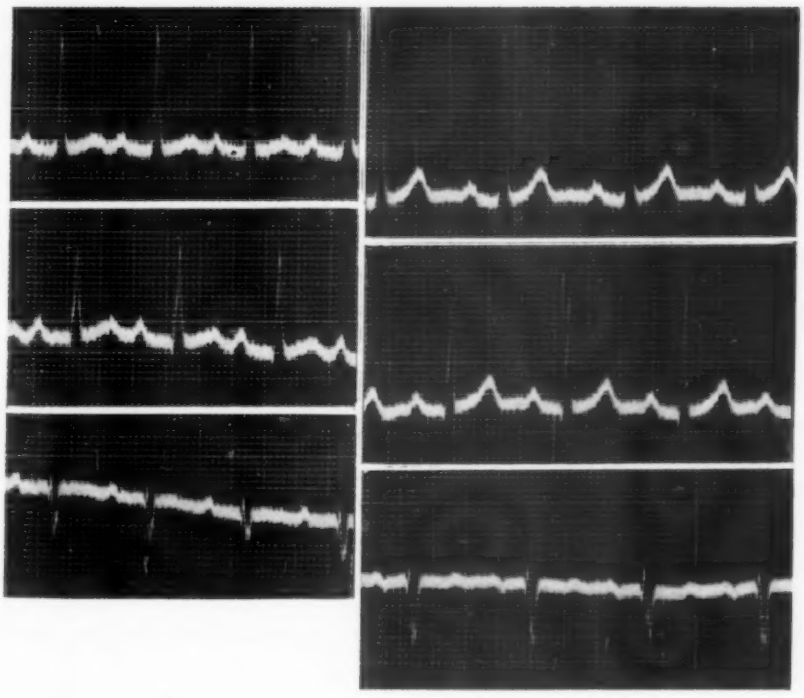


C D

FIG. 1. Case I.

The first was taken February 14, 1933 (figure 1*a*). In addition to the prolonged P–R interval seen frequently in acute infections of the rheumatic type, changes are seen in the S–T (or R–T) segment and in the T-wave. These changes consist of low origin of the R–T interval in Lead I; convex upward bowing of the R–T interval, Leads I and II; late cove shape T-wave inversion, Leads I and II, and isoelectricity of T_3. The second tracing was taken March 6, 1933 (figure 1*b*). In Leads I and II the R–T segment takes its origin from the descending limb of R before it reaches the isoelectric line and immediately slants upward to form the T-wave. In other words, there is no isoelectric R–T segment, the T-wave apparently springing directly from the descending portion of R. The third tracing was taken two weeks later (figure 1*c*). The R–T segment in Lead I, and to a less extent in Lead II, has a higher origin than normal. The descending limb of R barely reaches the isoelectric line. The last tracing (figure 1*d*), taken two months later, shows the T-wave to be of higher amplitude. There is still no period of R–T isoelectricity, the upstroke of T originating still a little above the isoelectric line on the downstroke of R.

Case II

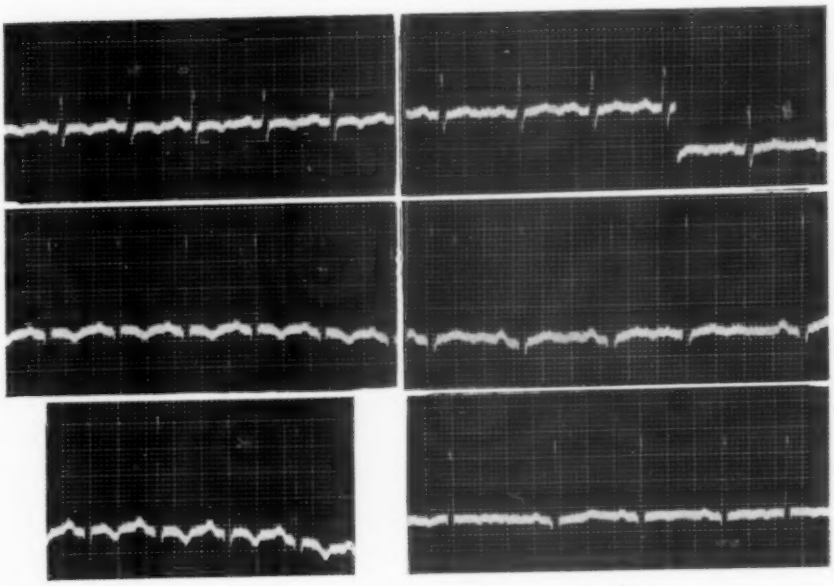
The patient was a mulatto boy of 16 years, admitted to the hospital April 7, 1933, complaining of pain in his chest and abdomen. This pain was of several days' duration and had been accompanied by fever. At the time of admission the pain was of maximum severity over the precordium. His temperature was 104.6°, pulse 112, and respirations 24 on admission. The past medical history was negative except for the usual childhood diseases. No rheumatic history of any kind could be elicited.

Examination showed a pale colored boy, not dyspneic and apparently not in pain. The tongue was coated; the cervical glands were palpable and tender. No petechiae were found on either skin or mucous membranes. On the day of admission there was thought to be some impaired resonance over the left chest, and in fact, roentgen-ray examination showed some evidence of an early bronchopneumonia. These signs disappeared, however, both clinically and by roentgen-examination within a few days. The apex beat of the heart was 7 cm. outside the midsternum in the fifth interspace. There was a gallop rhythm at the apex, and over a very limited area in the third left intercostal space a systolic murmur could be heard. The rest of the physical examination was negative.

On the day following admission a very pronounced friction rub was heard over the precordium. This diminished in intensity after the first day but could be heard faintly for several weeks. The temperature came down very rapidly but there continued to be a slight afternoon rise for about two and a half weeks. Premature beats were present at times and occasionally a systolic apical murmur could be heard. Neither of these findings was constant. At no time was there any joint involvement. The patient's convalescence was for the most part uneventful and he was discharged June 25, 1933 in good condition.

His treatment was symptomatic and aimed principally at the correction of his anemia. His blood count varied from 62 per cent hemoglobin, 3,500,000 red blood cells and 16,000 white blood cells on admission, to 88 per cent hemoglobin, 4,600,000 red blood cells and 8,700 white blood cells. Other laboratory examinations gave the following results: Wassermann and Kahn, negative; blood cultures, negative; stool examination, negative; sedimentation rate one month after admission was:

45 minutes .....25 per cent
1 hour .....36 per cent



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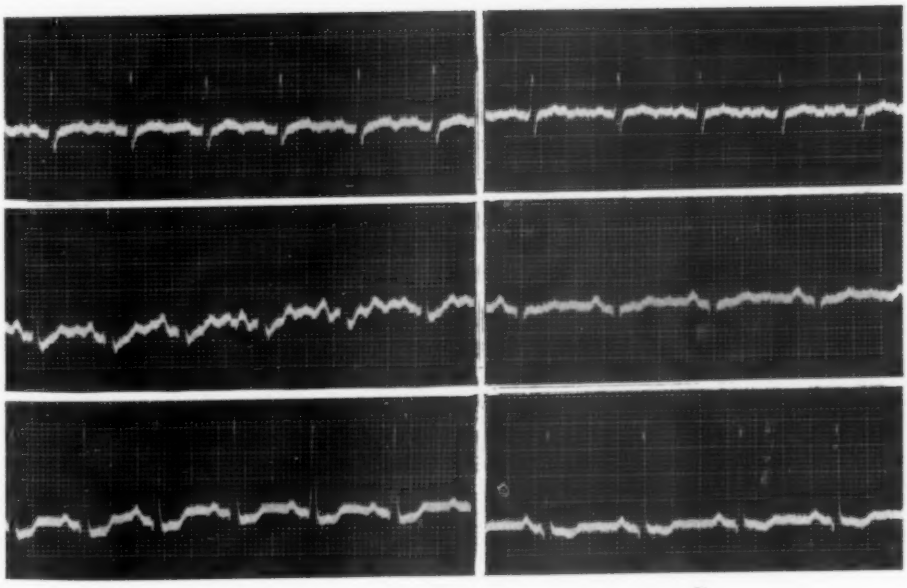

C D

FIG. 2. Case II.

The test was repeated just before discharge. The results were:

45 minutes ..... 4 per cent
1 hour ..... 5 per cent

The basal metabolic rate was plus 6 per cent. Urine examinations showed albumin and a few granular and hyaline casts at the time of admission. On discharge the urine was entirely negative. Fluoroscopic (orthodiagraphic) examination showed the cardiothoracic ratio to be 13:21 cm.

The first electrocardiogram (figure 2*a*) was taken April 25, 1933. It shows T-wave inversion in all three leads. The second tracing (figure 2*b*), taken two weeks later, shows low voltage of the T-waves in Leads I and II and isoelectricity in Lead III. Three weeks later a third tracing (figure 2*c*) shows an upward directed T_1 and T_2 and inverted T_3. All the T-waves originated below the basal line, and in the second and third leads there is a deep R–T depression. Three weeks later the fourth tracing (figure 2*d*) shows still an upward directed but low voltage T-wave in Leads I and II and there is much less R–T depression than was seen in the earlier picture. The last tracing (figure 3) was taken about one month later.

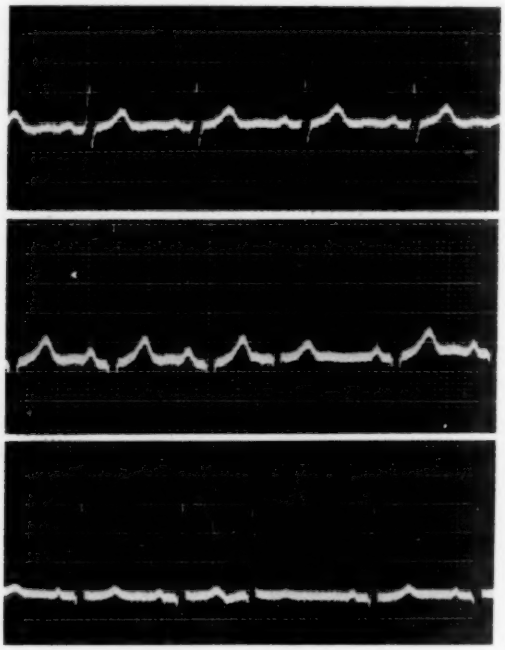

FIG. 3. Case II.

This is essentially normal except for auricular premature beats and for the fact that the R–T segment in Leads I and II arises directly from the downstroke of R without a normal isoelectric period.

CASE III

The patient was a male, aged 48 years. He was admitted to the hospital May 17, 1933, with the chief complaint of generalized joint pains and sore throat. The patient had been sick at home for three months before admission. His past history

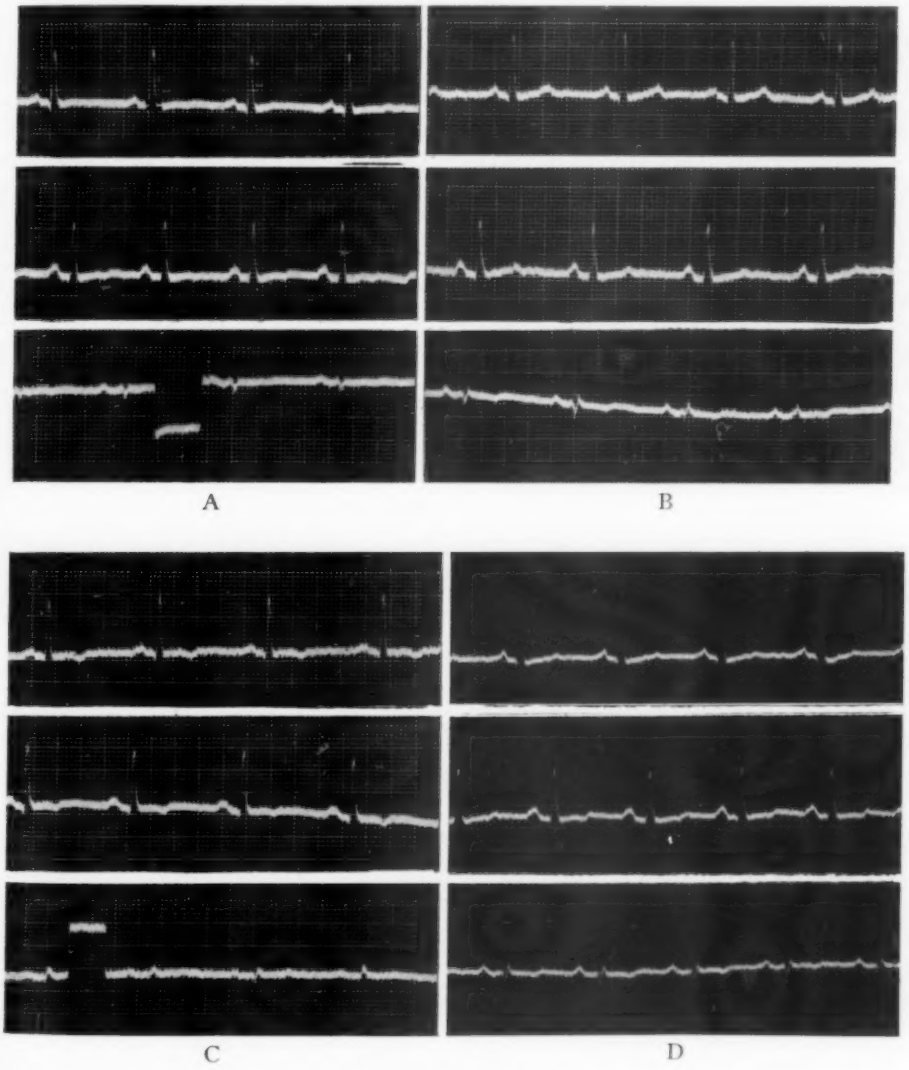

FIG. 4. Case III.

was negative for rheumatism but he had had scarlet fever and rather frequent sore throats in childhood. He had never had symptoms of cardiovascular disease.

On admission he was having joint pains and dypsnea. His teeth were in poor condition and his tonsils diseased. The lungs were clear. The apex beat of the heart was just outside the midclavicular line in the fifth interspace. The heart rate was 112, regular, and there was some accentuation of the second aortic sound. There

was a systolic murmur at the apex and base. The abdomen was negative. The joints of his fingers, left knee, left wrist, left elbow and shoulder were tender, swollen and hot, and there was thought to be effusion in the left knee joint. The temperature on admission was 101°.

On the day following admission, a to-and-fro friction rub was heard at the apex by one observer. This had disappeared 24 hours later and did not recur. The temperature came down to normal within about a week and the pains responded satisfactorily to salicylates. There was, however, an occasional afternoon rise of temperature of about one degree. On June 20, 1933, there was a more marked elevation for several days accompanied by the return of joint pains to a mild degree. Both fever and pain subsided after the patient was put back to bed for several days. Another rise of temperature occurred after tonsillectomy but was not in excess of what would be normally expected. There was an occasional fleeting return of joint pain, the most persistent being in one shoulder. This was effectively relieved by physiotherapy. The systolic murmur at the apex became more distinct as time went on but there was no other valvular involvement noted at any time. On admission the patient's blood count showed 73 per cent hemoglobin, 4,020,000 red blood cells and 16,250 white blood cells. One month later the count was 80 per cent hemoglobin, 4,130,000 red blood cells and 10,000 white blood cells. The urine was practically negative at all times. Sedimentation time a month after admission was:

45 minutes ..... 9 per cent
1 hour .....13 per cent

This was repeated a month later and gave practically the same results. Roentgen-ray examination showed the cardiothoracic ratio to be 17 : 32.5.

Electrocardiographic studies were made at intervals. The first tracings (figure 4*a*) were taken May 25, 1933, eight days after admission. They show a flattened T_1, slightly inverted T_2 and an isoelectric T_3. Three weeks later (figure 4*b*) the tracings show T_1 and T_2 to be upright. This was considered an improvement on the earlier ones, but on June 23, eleven days later (figure 4*c*) there was a distinct inversion of T_1 and T_2. It is interesting to note that this corresponded in time to the patient's secondary rise in temperature and return of joint pain. The fourth tracing (figure 4*d*), taken July 16, 1933, shows a return of T-waves to isoelectricity but with a tendency for the R–T segment in Lead I to originate below the basal line on the downward limb of the R-wave.

Discussion

The study of these three cases shows that in each of them the electrocardiogram has undergone changes during the course of an acute rheumatic infection. We have interested ourselves in only those changes which appear in the S–T or R–T segment or in the T-wave itself. The first case showed, during the acute infectious stage, T-wave inversion suggestive of coronary disease. This inversion showed constant improvement as the rheumatic infection cleared up, the T-wave assuming a definite upward direction. It must be noted, however, that even in the last tracing, which was taken more than two months after recovery, the T-wave arises abruptly from the downward limb of the R-wave and that there is a consequent lack of isoelectric

R–T interval. The second case presents similar characteristics. In the beginning there is a stage of sharp T-wave inversion, but within a period of a week or so, the T's become first isoelectric and eventually upright, although they remain of low voltage. However, even in the latest tracing, in which the T-waves are upright and of satisfactory height, there is still alteration of the R–T segment. The third case showed rapid improvement after the initial examination, the T-waves becoming upright and practically normal in contour in the second tracing. The third tracing, however, shows definite inversion in the two first leads. The patient had a reactivation of his infection at this time. With his eventual complete recovery, there was still isoelectricity of the T-waves. Since the R–T segment need not be absolutely flat in the electrocardiogram of normal individuals and since we have not available electrocardiographic tracings of the patients before the onset of the disease, it does not seem possible to ascribe to this finding a definite pathological significance. Pardee [1] believes that rarely these alterations may be permanent, due to fibrotic changes in the myocardium, or that they may be prolonged beyond the acute manifestations of the infection, indicating possibly a continuing low grade activity. A series of three cases is, of course, too small to enable one to draw conclusions regarding the frequency of these changes in rheumatic infection. They afford, however, evidence confirmatory of the reports of those observers who, in the past few years, have emphasized electrocardiographic abnormalities in rheumatic infections other than the better known conduction and rhythm alterations. In 1924, Cohn and Swift [2] reported studies on a series of 37 rheumatic patients, a number of whom showed similar R–T or S–T alterations, and they noted the similarity which some of these variations had to the type of T-wave found in recent coronary occlusion. They suggested at that time that this finding indicated disturbed muscular function such as might be caused by a transient Aschoff body. Bain and Hamilton [3] emphasized the importance of the electrocardiogram as a means of diagnosing myocardial involvement in the course of rheumatic infections. They analyzed tracings from 50 rheumatic children and found inversion of T-waves in one or more leads in eight cases, and depression of the S–T interval followed by a small T deflection in three cases. They likened this finding to a "digitalis T" occurring, of course, in the absence of digitalis. Rothschild, Sacks and Libman [4] express the belief that whereas the type of change in the electrocardiogram under discussion is not pathognomonic for acute rheumatic fever, it does occur oftener in this condition than in any other single pathological state. Reid and Kenway [5] had a rather high percentage of abnormal findings in their series of 26 cases. Of these, 11 showed S–T changes, and they were impressed also by the absence of S–T or R–T isoelectric periods. These observers believe that there is no correlation between the duration of joint symptoms and the duration of electrocardiographic changes, and they emphasize, as do other workers, the importance of the electrocardiogram in the early diagnosis of rheumatic myocarditis. McMillan

and Cook [6] found that in 48 cases studied, 10 showed slight changes in the R–T segment and 11 showed a negative T-wave. Porte and Pardee [7] reported on three cases with rheumatic pericarditis showing upward S–T convexity like that of a coronary thrombosis or narrowing. One of these cases at post mortem showed the left coronary artery to be thickened with an irregular subintimal proliferation. Whereas there was pericarditis present in these cases, the opinion is expressed that the abnormality in the tracings was due to inflammatory myocardial reaction, and that similar variations would appear in the absence of pericarditis.

The frequency with which pericarditis appears in the course of an acute rheumatic attack suggests the possibility that this condition in itself might be responsible for T-wave and R–T variations. Master [8] states that the so-called coronary type of T-wave may appear in patients with rheumatic pericarditis, and furthermore that occasionally pericarditis alone may produce a flat T-wave. He cites the example of tuberculous pericarditis and cancer of the pericardium where the underlying musculature is but little involved. Cowan,[9] however, in 1904, in a discussion of the pathological findings in the heart in acute disease, states the belief that pericarditis is a frequently unsuspected accompaniment of acute disease, and that the muscle in the vicinity of an inflamed pericardium is always degenerated. He says: "As a result of pericarditis, changes may occur in the adjacent connective tissue leading to an increase in its amount, or to its degeneration, both of which necessarily cause a further defect in muscle cells." Pardee,[1] while emphasizing the daily variations in T-wave and R–T interval during the acute stage of rheumatic fever, states: "A few patients, especially those with evidence of pericarditis show the peculiar upward convexity of the S–T interval followed by a downward T-wave, the 'coronary' T." The first case described in our report gave no clinical evidence of pericarditis. Of the other two, one presented the typical to-and-fro friction rub for only a very brief space of time, and at no time was there felt to be pericardial effusion in any of these patients. From a review of the literature and from our own observations we find that cases in which clinical evidence of pericarditis is lacking present T-wave alterations similar to those in which pericarditis is known to be present. Clerc, Lévy and Vialard [10] described isoelectricity or negativity of T-waves in 19 per cent of a series of 57 cases studied, and described one case in which the S–T interval had a high take-off in all leads. Shapiro [11] studied 119 cases of quiescent rheumatism in children and in adults, and concluded that changes in the S–T portion of the electrocardiogram are similar to, but of less frequent occurrence than those in active rheumatism. His control group of 50 normal cases presented only very negligible variations in repeated electrocardiographic studies. Vialard [12] found that out of 63 cases of active rheumatism studied, only 14 presented no electrocardiographic alterations and that there were T-wave changes in 18 of these cases. He did not, however, note characteristic alterations of the S–T segment other than those connected

with abnormalities of the QRS or T. He emphasized the importance of the electrocardiogram for early diagnosis of rheumatic disease, especially when its appearance is atypical such as in cases presenting pulmonary or abdominal symptoms. Vialard quotes from a French clinician, Besnier [13] who, in 1877, wrote so significantly of the involvement of the myocardium in acute rheumatic fever, that we have felt it pertinent to present a translation of his remarks at this point: "The heart muscle is generally, one may say always, affected to some degree in the course of acute articular rheumatism. This affection may represent an advanced degree without any considerable concomitant lesion of the endocardium or pericardium. If the heart is affected by endocarditis or pericarditis then there is even much more reason to assume that the whole heart is diseased. This fact one has indeed quite forgotten and one is too much inclined to assume that all organic lesions of the heart in rheumatic disease have their origin in the endocardium and pericardium. One might call this whole condition rheumatic carditis, if this expression does not sound too antiquated."

Heiles [14] definitely states that a curving of the R–T segment, either convexly or concavely, to any marked degree cannot occur in a normal heart. Having noted alterations during rheumatic infections similar to those of coronary disease, he accounts for the upward convexity or concavity on the ground of hyperfunction or hyperirritability of a portion of the ventricular muscle. He believes that if the injury to the muscle is of an inflammatory nature, the ventricular complexes will return to normal in a relatively short time. But if there is an area of necrosis such as follows an occlusion of a coronary artery, there will be a lasting dysfunction of the necrosed area. He notes that rheumatic infection is not followed by a sharp T-wave inversion coming late after the time of injury such as is caused by the scarring which follows thrombosis. Slater [15, 16] published three cases which gave the clinical signs of coronary occlusion. The first two cases showed first an elevation of the R–T interval in Leads I and II; this was followed by inversion of the T-wave, which eventually became upright again. In the third case, which had several recurrent attacks, the following changes were observed in addition: Absence of isoelectricity of the R–T segment, flattening of the T-wave, low take-off of the S–T segment in Lead II.

Sebastiani [17] presented a statistical study of 26 cases showing that in 15 of these cases some change in the S–T segment occurred in one or more leads; that in one or more leads a negative T-wave appeared in 11 cases; a diphasic T in seven cases; a low voltage T in 16 cases; that there was absence of T-wave in one case; that the T began above the basal line in at least one lead in four cases, and that the ascending branch of the T-wave was oblique and thickened in one or more leads in four cases. Additional statistical data on this subject are given by Lukomski [18] who studied 100 cases of initial or recurrent attacks of acute rheumatic fever and who found negative T-waves in 13 of these cases. He noted that this change occurred usually at the height of the disease and that in eight of the cases the T

became positive again within 10 to 30 days. He noted furthermore the similarity of the upward directed S–T period to that caused by coronary disease but believes these changes are due to Aschoff bodies in the myocardium. Lian and Calcena [19] reported that three out of 28 cases studied showed negativity of T-waves in one or more leads, but did not note alterations of the S–T interval. Master and Romanoff,[20] in a recent publication, reported that 53 out of a series of 63 cases of acute rheumatic fever studied, showed some variation in the RST portion of the electrocardiogram. T-wave changes occurred in 29 of these.

We are convinced from a review of the literature on this subject, as well as from our own observations, that R–T or S–T alterations of the electrocardiogram are as characteristic, though not pathognomonic, and probably of quite as frequent occurrence in acute rheumatic fever as the better known alterations in conduction and rhythm. Not only is T-wave inversion or isoelectricity of diagnostic import, but in addition the alterations in the point of T-wave origin with a consequent deformity, shortening or entire absence of an isoelectric R–T segment may be characteristic. These electrocardiographic deformities which are so similar to the deformities of coronary disease suggest that the underlying pathological processes should be looked for in the coronary circulation and a consequent interference with myocardial blood supply, a view-point which has been emphasized by Slater.[15, 16]

The rheumatic process manifests itself in the heart as a part of a general mesenchymal disease of the organism. The course of the disease shows different stages, which later on may occur simultaneously. The first, an acute stage, is a degenerative-exudative one. It is characterized by edema and fibrinoid swelling of the matrix of the connective tissue; necrosis of muscle fibers and lymph-leukocytic infiltration is often seen. The second, a subacute stage, is often characterized by mesenchymal cell proliferation, the formation of a granuloma, though a diffuse process without this granulomatous formation may take place. The last, a chronic stage, is the process of healing with scar formation.

In this connection the pathology of only the acute and subacute stage is considered and only as far as it concerns the vessels of the heart. The affection of the aortic wall is only mentioned when coronary opening involvement is explicitly mentioned, though rheumatic aortitis (Klotz,[21] Pappenheimer and VonGlahn,[22] Breitenecker [23]) may often cause coronary narrowing during the phase of exudative swelling. No mention is made of the degeneration of muscle fibers or of embolic infarction which often accompanies endocarditis (Aschoff,[24] Takayasu [25]).

The following chronological survey will demonstrate, without further comment, the anatomical substratum which may be encountered during the acute and subacute stage. Needless to say, the degree of the pathologic lesions may vary enormously, and the extent of functional interference will

differ correspondingly. This functional interference may find its expression in the electrocardiogram.

ROMBERG [26]—Multiple hyaline thromboses of small arteries and veins. Infiltrative periarteritis.

RABÉ [27]—Proliferative endarteritis of small arteries, often with considerable reduction of their lumen. "Mésartérite parenchymateuse."

ASCHOFF [28]—All coats of small and medium-sized arteries may be involved in the process of submiliary nodule formation.

GEIPEL [29]—Rheumatic nodules occasionally narrowing the lumen of vessels. Endarteritis of small and medium-sized arteries, the subendothelial fibrinous exudate narrowing or occluding the lumen of the vessels.

COOMBS [30, 31]—Nodules in media, with unilateral narrowing of the lumen of a vessel. Nodular periarteritis. Inflammatory patches at the root of the aorta.

KLOTZ [21]—Periarteritis of small vessels.

FAHR [32]—Invasion and semilateral destruction of vessel walls by nodules. Complete degeneration in focal areas of media.

WÄTJEN [33]—Nodular infiltration of vessel walls with thrombi in diseased vessels.

COOMBS [34]—Turgescence of the endothelial cells of capillaries and arterioles. Endothelial proliferation with disappearance of the lumen of the vessel. Thromboses in capillaries, small arterioles and venules and in a main coronary artery.

SWIFT [35]—Endarteritis with swelling and proliferation. Narrowing of vessel lumen by nodules. Partial or complete thrombotic occlusion.

MCCALLUM [36]—Wall destruction of arterioles and of large coronary sinuses with thromboses.

PAPPENHEIMER and VONGLAHN [22]—Inflammatory plaque in the beginning of the left coronary artery. Parietal thrombus in a large coronary branch. Semilateral narrowing of lumen of a vein due to subendothelial infiltration.

PERRY [37]—Panarteritis of coronary arteries and their main branches; patchy thickening of intima, degeneration and inflammation of media, inflammatory infiltration in adventitia.

KLINGE [38]—Marked fibrinoid swelling of the intima of small arteries and veins, with narrowing of the lumen. Nodules in all wall layers of arteries and veins; intimal cushions.

KLINGE and VAUBEL [39]—Almost complete occlusion of arteries and veins by swelling and cell proliferation of intima.

BREITENECKER [23]—Intima proliferation and thrombosis occludes the right coronary opening and narrows down the left one.

Summary

Three cases are reported which showed during the course of a rheumatic infection the following electrocardiographic changes: First, of the S–T (R–T) segment: a low or high take-off, a convex upward bowing, a depression, an absence of the isoelectric portion. Second, of the T-wave: isoelectricity, low voltage, origin below the basal line, simple inversion, cove-shaped inversion. The electrocardiogram approached a normal form if the rheumatic infection cleared up but even at the stage of complete recovery there was in one case persistence of isoelectricity of the T-waves. In none of the three cases was evidence of a pericardial effusion present. These changes, though not pathognomonic for rheumatic fever, occur rather commonly, as a review of the literature shows. Anatomical studies from the literature are reported which support the conception that the S–T (R–T) and T changes express an alteration of the musculature caused by the effects of the acute infection on the coronary circulation.

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THE GALACTOSE AND UROBILINOGEN TESTS IN THE DIFFERENTIAL DIAGNOSIS OF OBSTRUCTIVE AND INTRAHEPATIC JAUNDICE*

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THE enigma which may confront the internist in the differential diagnosis between mechanically obstructive and intrahepatic (toxic or infectious) jaundice, occurring particularly in individuals beyond the age of 35, is indeed a familiar though often disconcerting situation. Bauer [1] has often emphasized his contention that the galactose tolerance test provides an exact differentiation between these two types of jaundice, for his results were consistently negative in the obstructive form and distinctly positive in the intrahepatic form, unless the latter was of a very mild nature. The observations of other German investigators tended in the main to corroborate these findings. Davies,[2] although agreeing with these results, felt that no interpretation should be based on this single test of liver function.

In this country, little clinical recognition was accorded these contributions until the papers of Shay and Schloss [3, 4, 5] appeared, corroborating Bauer's earlier conclusions. They explained these differences in galactose tolerance on a pathologic basis. In the toxic or intrahepatic form an acute or subacute, diffuse, hepatic, parenchymal damage occurs with a resultant derangement in the carbohydrate function; in the obstructive form, in which hepatic destruction is progressing slowly, the regenerative and reserve powers of the liver permit of a normal carbohydrate function. Recently, in a study of 68 confirmed cases of obstructive jaundice, Banks, Sprague and Snell [6] found positive results in one-third of the benign group and in approximately 46 per cent of the malignant group; while of 18 cases of acute or subacute intrahepatic jaundice, 84 per cent were positive. They felt that the galactose test might be of value in doubtful cases. Latterly, Tumen and Piersol [24] found the test "practically always negative" in obstructive jaundice and positive in the majority of cases of toxic hepatitis and catarrhal jaundice. They regarded it as of definite diagnostic value.

The use of the urobilinogen test in clinical jaundice is based upon the generally accepted view [7, 8] that urobilinogen is formed from bilirubin by the action of certain putrefactive bacteria of the intestine and is eliminated in part through the kidneys. The disappearance or absence of urobilinogen from the urine in obstructive jaundice has frequently been noted [1, 9, 11, 16, 17, 18, 19] since the early observation of Müller,[7] yet one is able to cull from the literature only a few references directing attention to its potential diagnostic value. Bauer [16, 20] and Wallace and Diamond [16, 17, 18] found excessive

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amounts of urobilinogen in the urine during the beginning and end of catarrhal jaundice, and only traces or a total absence during the height of the jaundice, when very little if any bile is being excreted into the intestine. From their studies, Wallace and Diamond,[16,17,18] and later Davies,[2] concluded that the presence of urobilinogen in the urine points to an intrahepatic jaundice, whereas its constant absence bespeaks an obstructive jaundice.

In the present investigation, an attempt has been made to evaluate the respective merits of these tests; also to ascertain any relative superiority and to determine the virtue of supplementing one test by the other.

Material and Methods

This report deals with the results of studies conducted on a total of 30 patients. Of this series, 16 were cases of obstructive jaundice, which in four was due to a stone and in 12 to a malignant process. The diagnosis in 15 of these cases was confirmed either by necropsy or by operation, and in the other one the clinical diagnosis was definite. Of the remaining 14, there were 12 patients with acute or subacute intrahepatic jaundice; in one of these, the diagnosis was based upon necropsy studies, and in 11 upon the clinical history, the signs and the course which led to ultimate complete recovery. Of the remaining two patients with chronic intrahepatic jaundice (cirrhosis), the diagnosis in one was confirmed at necropsy. Except for these two cases of cirrhosis, only those patients in whom the differential diagnosis between obstructive and intrahepatic jaundice was of primary importance, were selected. The course of the jaundice was followed by repeated determinations of the icterus index. In all cases, studies were instituted as soon as it was feasible, in order to facilitate an early diagnosis.

The technic of the galactose test was identical with that described by Shay, Schloss and Rodis[3,4,5] and was based upon the original work of Bauer. After an overnight fast, the patient voids and the specimen is saved as a control. He is then given exactly 40 gm. of pure galactose, dissolved in 500 c.c. of water and flavored with a few drops of lemon juice. Urine specimens are collected hourly for five hours and placed in separate containers. During the period of the test the patient may drink water if he desires, but nothing else. Each specimen is tested for sugar by the Benedict qualitative method. Those specimens which are positive are mixed and the total amount of sugar is determined by the Benedict quantitative method. An excretion of more than 3 gm. of galactose was considered indicative of an intrahepatic jaundice. No diabetics were encountered in this series.

The Ehrlich's aldehyde reaction was chosen for the detection of urobilinogen. The technic consisted of adding 1 c.c. of Ehrlich's reagent (2 gm. paradimethylamidobenzaldehyde in 100 c.c. of 20 per cent HCl) to 10 to 15 c.c. of urine. If positive, a red color appeared within 3 to 5

minutes. The Wallace and Diamond method of quantitation was used in the early part of this work, but it was soon found that the quantity could be expressed satisfactorily in terms of 1 plus to 4 plus, depending on the depth and rapidity of color formation. Normally, urobilinogen excretion, although varying from hour to hour, is greatest when the metabolic processes are at their height, usually in the afternoon. Accordingly, urine was obtained before or shortly after lunch and the test was applied immediately. In those cases in which urobilinogen was absent, daily examinations were made and at least two late afternoon specimens were examined. During the period of observation, no patient received antipyrine or hexamethylamine and the absence of acetone from the urine was ascertained, thereby eliminating pseudo-positive reactions.

Results

Acute and Subacute Intrahepatic Jaundice. In table 1 are recorded the results of observations on 10 patients with "catarrhal jaundice," one with cinchophen poisoning and one with alcoholic steatosis. In the majority, the age was beyond 35, a circumstance which is of special interest to us because of its relationship to the so-called "cancer age." The duration of the icterus from the time of its inception to the day of the galactose test varied from five days to six weeks with a mean average of 17 days. In two patients of this group (cases 6 and 10), the jaundice was already subsiding at the time that the galactose test was applied, thereby accounting for the normal response. Of the remaining 10 patients, seven excreted galactose in amounts greater than the adopted maximum of normal; in the other three, the excretion was well within normal. It is noteworthy that the jaundice in these latter three cases (cases 2, 9 and 12) was at its maximum at the time of the test and that it was particularly intense in case 9. The greatest excretion encountered (6.4 gm.) was observed in case 5, at a time when the jaundice had begun to subside. (Unfortunately this patient was not seen when the icterus index was at its peak.) From these results there appears to be no relationship between the degree of icterus in different persons and the amount of galactose excreted.

Case 12 is worthy of special comment, for it exemplifies the point made by Shay, Schloss and Rodis: namely, that an extensive and very diffuse process is essential for the production of an abnormal galactose output. Even though the galactose test was normal, the liver sections showed a marked alteration of the parenchyma with most of the liver cells filled with large fat droplets and the remaining ones distinctly swollen.

In all of the 12 cases, urobilinogen was detected in the urine at one time or another. In three instances it was consistently absent during the early period of observation but in none was it absent longer than seven days. It always appeared later in gradually increasing amounts. It must be emphasized that it is of the greatest importance to examine fresh specimens

TABLE I
Acute and Subacute Intrahepatic Jaundice

TABLE I
Acute and Subacute Intrahepatic Jaundice

Case	Age	Sex	Duration of Jaundice	Icterus Index	Galactose Excretion	Urobilinogen*	Diagnosis**	Comment
					(Gm.)			
1	28	M.	6 weeks	150	4.45	Trace	"Catarrhal Jaundice"	Urobilinogen ++++ one week after galactose test.
2	48	M.	15 days	93	1.80	0+ to ++++	"Catarrhal Jaundice"	Urobilinogen absent for 1 week. No oliguria, vomiting, diarrhea or dehydration.
3	27	M.	2 weeks	77	4.00	Trace	"Catarrhal Jaundice"	– – – –
4	27	M.	9 days	118	4.90	0+ to ++++	"Catarrhal Jaundice"	Urobilinogen absent for 4 days.
5	41	M.	15 days	45 (Subsiding)	6.40	+; later ++++	"Catarrhal Jaundice"	Icterus index 90, 10 days before galactose test. Common duct stone strongly considered.
6	38	M.	2 weeks	37 (Subsiding)	0.00	Trace to +	"Catarrhal Jaundice"	Icterus index 64, one week before galactose test.
7	43	M.	11 days	93	4.50	+++	"Catarrhal Jaundice"	– – – –
8	45	M.	6 days	60	4.29	++++	"Catarrhal Jaundice"	– – – –
9	38	M.	5 days	155	0.00	Trace Later +++	"Catarrhal Jaundice"	No oliguria, vomiting, diarrhea or dehydration.
10	55	M.	25 days	46 (Subsiding)	0.80	+	"Catarrhal Jaundice"	Urobilinogen + for 10 days before galactose test was done.
11	44	M.	3 weeks	126	3.60	++	Cinchophen Poisoning	– – – –
12	36	F.	4 weeks	75	0.00	0+	Alcoholic Steatosis of Liver. (P.M.)	History of alcoholism and of biliary colic. No oliguria, diarrhea, vomiting or dehydration.

* + indicates urobilinogen in urine at one time or another.
0+ indicate urobilinogen consistently absent at first and later present.
** All are clinical diagnoses except case 12.
P.M. Postmortem.

immediately and repeatedly. In cases 2 and 9, which yielded a normal galactose response, such repeated urobilinogen studies proved in retrospect to be of inestimable value, for although these cases simulated catarrhal jaundice clinically, a suggestive history of biliary colic in the face of a negative galactose test (pointing to an obstructive jaundice) proved misleading, and only the urobilinogen excretion curve together with the subsequent clinical course revealed the true nature of the illness. Another case in point attesting its value and indicating the need of a more universal application of the urobilinogen test, is that of patient 10, a man of 55 who presented himself with the symptoms of a painless, progressive jaundice of four weeks' duration, accompanied by a loss of 20 pounds, and concerning whom no definite decision between catarrhal jaundice and carcinoma of the head of the pancreas could be reached. An exploratory laparotomy was deemed advisable; but, because of a consistently positive urobilinogen test, operation was postponed. The subsequent course, characterized by a decline in the jaundice with complete recovery, justified such conservative management.*

Chronic Intrahepatic Jaundice. A proved case of cholangiolitic cirrhosis and a clinical case of biliary cirrhosis are included in this category (table 2). The jaundice was intermittent in each instance, and in one had been noted as long as three years before admission. In both, the galactose tolerance test was normal irrespective of the degree of jaundice, and the urobilinogen test was strongly positive.

Obstructive Jaundice. This group is represented by 16 cases, in four of which the common duct was occluded by a stone and in 12 by an extrahepatic malignancy (table 3). It is particularly in the latter type of obstruction, so frequently painless in onset, that keen interest attaches to the correct diagnosis and especially prognosis. The age incidence in the cases of malignancy varied from 36 to 77, and the jaundice was of two weeks' to five months' duration, the average being approximately two months. In all 16 cases of obstructive jaundice the galactose excretion was normal. This includes a case of intermittent hepatic fever with jaundice of seven and a half months' duration.

In 10 of the 12 cases of malignancy, urobilinogen was not detected during the entire period of observation; in one, although present in traces during the first five days, it subsequently disappeared and remained consistently absent; in another (case 20), traces were always found, but in this instance the obstruction had not yet become complete. In the cases of obstruction by a stone, urobilinogen was present in varying amounts at one time or another. It is apparent from case 20 that difficulty may be encountered in differentiating an obstructing stone from incomplete occlusion by a new growth, in which instance we must rely upon a carefully

* Because of certain technical difficulties in this case, the galactose test could not be performed when the jaundice was at its maximum. Later, the response was normal but by this time the icterus index was much lower.

TABLE II

Chronic Intrahepatic Jaundice

Case	Age	Sex	Duration of Jaundice	Icterus Index	Galactose Excretion	Urobilinogen	Diagnosis	Comment
13	43	M.	6 months	18	(Gm.) 2.50	++++	Cholangiolitic cirrhosis with chronic splenic tumor. (P.M.)	Jaundice for 6 months before galactose test. Intermittent and remittent jaundice for 3 years.
14	32	M.	9 weeks	53	0.65	++++	Biliary cirrhosis. (Clinical)	Recurrent ascites. Intermittent jaundice. Liver greatly enlarged. Moderate splenomegaly.

TABLE III

Obstructive Jaundice

Case	Age	Sex	Duration of Jaundice	Icterus Index	Galactose Excretion	Urobilinogen	Diagnosis	Comment
					(Gm.)			
15	70	M.	4 months	67	1.37	0	Carcinoma of head of pancreas; obstructive biliary cirrhosis. (P.M.)	Ascites
16	64	M.	3 weeks	76	2.20	0	Carcinoma of common bile duct; obstructive biliary cirrhosis. (P.M.)	—
17	77	M.	Unknown	35	0.80	0	Carcinoma of duodenum; compression of common duct. (P.M.)	—
18	55	M.	5 months	185	1.20	0	Carcinoma of head of pancreas; compression of common duct. (P.M.)	—
19	72	F.	5 weeks	90	1.08	0	Carcinoma of head of pancreas; compression of common duct. (P.M.)	—
20	36	M.	3 weeks	65	2.16	Trace	Carcinoma of common and hepatic ducts. Gall-bladder markedly distended. (Operation.)	Clinical picture of cholelithiasis.
21	67	M.	15 days	63	1.00	Trace 0	Carcinoma of pylorus with metastases to hilus nodes; compression of hepatic duct. (Op.)	Urobilinogen in traces for 5 days. None thereafter.
22	50	M.	15 days	115	0.00	0	Carcinoma of head of pancreas; metastases to and distention of gall-bladder. (Operation.)	—
23	53	M.	6½ weeks	65	1.50	0	Carcinoma of head of pancreas. (Op.)	—

TABLE III (*Continued*)

Case	Age	Sex	Duration of Jaundice	Icterus Index	Galactose Excretion	Urobilinogen	Diagnosis	Comment
					(Gm.)			
24	55	M.	2 weeks	72	1.00	0	Extensive carcinoma of gall-bladder and extrahepatic ducts. (Operation.)	—
25	71	M.	15 days	75	0.55	0	Carcinoma of head of pancreas; metastases to liver. (Operation.)	—
26	68	M.	3 months	70	0.40	0	Carcinoma of gall-bladder. Constriction of hepatic duct by infiltrating tumor. (P.M.)	—
27	68	M.	4 months	65	1.30	+++	Large irregular stone in common duct. Marked chronic cholecystitis; stones; cirrhosis. (Operation.)	—
28	63	M.	4 weeks	123	1.40	+ to ++	Impacted stone in common duct; obstructive biliary cirrhosis. (Operation.)	Intermittent jaundice 15 years. Ascites. Splenomegaly.
29	28	M.	17 days	123	0.00	Faint trace	Stones in common duct. Marked chronic cholecystitis with cholelithiasis and extensive adhesions around ducts. (Operation.)	—
30	52	F.	7½ months	43	0.00	Variable. 0 to ++++	Stone in common duct. (Clinical diagnosis.)	Typical Charcot's intermittent hepatic fever.

taken history along with the usual clinical and laboratory studies, and, as emphasized by Piersol, Bockus and Shay [25, 26] and others, upon the presence or absence of cholesterol and bilirubin-calcium crystals in the bile; or, failing in these, prolonged observation of the urobilinogen excretion (case 21) may give us information of a decisive nature.

The persistence of traces of urobilinogen or its subsequent reappearance in experimentally produced complete biliary obstruction has been noted by Wilbur and Addis [9] and by others.[11, 16, 17, 18, 21] While these findings did not obtain in our clinical series, such possibilities deserve recognition. From the recent experimental work of Salmon [21] they appear to be dependent upon the blood bilirubin concentration and the duration of the obstruction. Significant in this respect too, is the presence of bilirubin in the intestinal mucosa of such animals, noted by Gerhardt [22] and by others [11, 23] and presumably indicating a slight leakage of bile pigment through the intestinal wall into the lumen, probably through the casting off of epithelial cells.

Comment

From the present study of 30 selected cases of jaundice it is apparent that the galactose test, supplemented by the urobilinogen test, may furnish us with diagnostic data very often of an unequivocal nature. Indeed, Bauer [1e] has found these two tests of distinct value, and Davies has referred to the advantage of combining the galactose test with other tests of liver function, including the urobilin test.

In all of our cases of obstructive jaundice, either benign or malignant, irrespective of the duration of the jaundice, the galactose test was negative. In those with complete obstruction, the Ehrlich's aldehyde reagent failed to reveal the presence of urobilinogen in the urine; when the obstruction was incomplete but of a constantly increasing degree, urobilinogen was always detected, though never present in more than traces. In acute or subacute intrahepatic jaundice, if we exclude those cases in which negative results were obtained when the icterus was already subsiding, the galactose test was found positive in seven of the remaining 10. In all cases with this type of jaundice, urobilinogen was present in the urine in variable amounts at one time or another, ultimately appearing in large quantities if the period of observation was sufficiently prolonged.

It is in those cases which do not conform to the rule of the majority that the combined use of the urobilinogen and the galactose tests appears to be of reciprocal value and finds its greatest field of usefulness. Cases 2 and 9 are representative of what was interpreted to be obstructive jaundice, principally on the basis of the normal galactose response, but in which the final picture was elucidated by the repeated, supplementary, urobilinogen studies. Contrariwise, in case 20, an instance of incomplete obstructive jaundice with constant traces of urobilinogen in the urine, it was the nega-

tive galactose test which disclosed the true nature of the morbid process. From this point of view, the report of Banks, Sprague and Snell is of practical interest to us, for although their high percentage of positive results with the galactose test in the obstructive group is at variance with the findings of Bauer, Davies, Shay, Schloss and Rodis, Tumen and Piersol and also with those of the present study, it would seem that the urobilinogen test might be of considerable value in such cases. Finally, we must recall the possibility that a secondary ascending infection of the biliary tract by certain reducing bacteria,[15, 16, 17, 18] occurring in a case of complete occlusion, may be accompanied by the appearance of urobilinogen in the urine and hence lead us to suspect an intrahepatic jaundice. In such cases the galactose test if negative may be of significant utility.

We may conclude from this study that the urobilinogen and the galactose tests taken individually are truly worthy of clinical acceptance and application. It is more difficult to make final deductions concerning their relative superiority. Yet from an analysis of these cases, the urobilinogen test appears to be more reliable than the galactose test in differentiating intrahepatic from obstructive jaundice. Again, the several factors of error, such as oliguria, dehydration, vomiting and gastric stasis, which may preclude the use of the galactose test or militate against a correct interpretation of its excretion,[6] do not seem to play a significant rôle in the outcome of the urobilinogen test. The combined use of these tests, however, may provide us with more decisive information and contribute to a more intimate understanding of the nature of the underlying disease.

Summary

1. Galactose and urobilinogen determinations were made on 12 cases of acute and subacute intrahepatic jaundice, two cases of chronic intrahepatic jaundice and 16 cases of obstructive jaundice.

2. Seven cases of acute and subacute intrahepatic jaundice yielded abnormal galactose responses. Of the remaining five with a normal response, in two the jaundice was already subsiding when the galactose test was performed. Urobilinogen was detected in the urine of all cases of this group at one time or another.

3. The galactose test was normal and the urobilinogen test was strongly positive in both cases of chronic intrahepatic jaundice.

4. In the obstructive group the galactose test was uniformly negative. Urobilinogen was absent from the urine of all cases of complete obstruction.

5. Individually, these tests are worthy of clinical acceptance, although from this study the urobilinogen test seems the more reliable.

6. Utilization of both the galactose and the urobilinogen (urinary) tests is advocated in the routine clinical study of jaundice.

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THE PLEURAL AND PULMONARY COMPLICATIONS OF CARCINOMA OF THE ESOPHAGUS*

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Introduction

One of the ways carcinoma of the esophagus may disguise itself is in the form of a chronic pleural or pulmonary infection. This usually is the result of a perforation of the esophagus into the trachea, bronchi, mediastinum, lung or pleura. In some cases, food or fluid is aspirated into the air passages due to the obstruction of the esophagus, or a necrotic lymph node which is the site of metastases may perforate into both the lung and esophagus producing a fistula. In other cases, the trachea or bronchi may be obstructed due to the invasion of the tumor growth or as a result of pressure from enlarged lymph nodes which are the site of metastases. In these, the complications of tracheo-bronchial stenosis arise. At this time, the observations of 17 cases of carcinoma of the esophagus in which there were pleural or pulmonary complications are recorded.

Before proceeding with the details of the cases, it is necessary to point out that the site and frequency of pleuro-pulmonary complications in carcinoma of the esophagus will naturally depend upon the exact type of tumor and its location. It is well known that squamous cell carcinoma of the esophagus ulcerates frequently, and in these cases perforation is seen commonly. Adenocarcinoma of the esophagus, on the other hand, ulcerates less often and produces obstructive symptoms earlier.

The upper third of the esophagus is in close contact with the trachea, the carotid arteries and the recurrent laryngeal nerve. In the medial third, it is in close contact with the trachea, left bronchus, the intercostal arteries, the thoracic duct, the hemiazygos veins, aortic arch, left subclavian artery and left pleura. In the lower third, it is in close contact with the left auricle of the heart, the pericardium and descending thoracic aorta.

It is of some significance that tumors of the esophagus commonly metastasize to the mediastinal lymph nodes. These enlarged nodes may invade the lung or trachea, compress the esophagus at some distance from the primary growth or cause unilateral or bilateral paralysis of the recurrent laryngeal nerves. In a few cases, the cancer may invade the veins so that venous thrombosis or widespread metastases in the lungs or elsewhere are observed.

A summary of the cases is presented in table 1.

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TABLE I
Summary of 17 Cases of Carcinoma of the Esophagus with Pleural and Pulmonary Complications.

Case No.	Location of Carcinoma	Site of Perforation	Physical Signs	Anatomical Lesions	Fever	W.B.C.	Duration of Illness	Symptoms	Remarks
1 ♂ 70	Middle third	Left bronchus	Pleural effusion. Left thoracic cavity	Bronchopneumonia left lower lobe.	98.6–101.5°	16,800	7 months	Epigastric pain. Dysphagia. Coughing following ingestion of food. Hematemesis.	Hematemesis caused death.
2 ♂ 62	Middle third	Trachea	Bilateral bronchopneumonia	Bilateral bronchopneumonia.	98.6–100.0°	19,800–20,720	5 months	Epigastric pain. Dysphagia. Regurgitation of food. Coughing following ingestion of food or water. Purulent sputum.	Recurrent laryngeal paralysis.
3 ♂ 50	Middle third	Trachea	Mediastinal widening. Râles over both lower lobes.	Bilateral suppurative bronchopneumonia.	99–101°	12,000	5 months	Dysphagia. Coughing following swallowing. Pain in mid-sternum.	
4 ♂ 72	Middle third	Left bronchus	Pleural effusion: Left pleural cavity. Bronchopneumonia left lower lobe.	Diffuse bronchopneumonia left lower lobe. Pleural effusion.	99–102.5°	16,800–32,000	7 months	Pain in epigastrium. Dysphagia. Coughing following swallowing.	Cirrhosis of liver. Metastases to glands at hilum of left lung. Hematemesis caused death.
5 ♂ 53	Middle third	Trachea	Superior mediastinal mass.	Bilateral bronchopneumonia.	101–102°	9,000	9 months	Hoarseness. Dysphagia. Coughing following swallowing.	Recurrent laryngeal paralysis; right side. Mass in superior mediastinum. Enlarged glands above right clavicle. Perforation observed in trachea with bronchoscope.
6 ♂ 59	Lower third	Left lower lobe of lung	Lung abscess left lower lobe. Solidification of left lower lobe.	Lung abscess left lower lobe.	99–103°	18,000–22,000	9 months	Dysphagia. Pain in chest. Cough. Copious amounts of sputum.	Clubbed fingers. Elastic tissue in sputum.
7 ♂ 70	Middle third	None	Signs of solidification of left upper lobe.	Lung abscess left upper lobe. Narrowing of trachea and left superior bronchus.	99–102°	12,000	8 months	Pain beneath manubrium. Coughing after swallowing.	Fatal hematemesis. Ulceration of vessels.
8 ♂ 68	Upper third	None	Signs of solidification and cavity formation in left upper lobe.	Lung abscess left upper lobe. Direct extension of infection from cancer to lung.	99–101°	10,000	7 months	Loss of weight. Substernal pain. Cough and expectoration. No dysphagia.	Metastases to lung—pleura—peritoneum.

TABLE I (*Continued*)

Case No.	Location of Carcinoma	Site of Perforation	Physical Signs	Anatomical Lesions	Fever	W.B.C.	Duration of Illness	Symptoms	Remarks
9 ♂ 50	Lower third	Right lung and pleura	Signs of solidification and fluid—right lower lobe.	Pneumonia with abscess formation right lower lobe. Empyema right pleural cavity.	99–102.5°	14,000	7 months	Dysphagia. Cough. Epigastric pain. Coughing following swallowing. Pain in right chest.	
10 ♂ 52	Lower third	Right lung	Râles and dullness over right lower lobe.	Abscess cavity in upper part of right lower lobe.	100–102°	13,000	2 months	*No dysphagia.* Cough with copious amounts of sputum.	
11 ♂ 63	Upper third	None	Solidification of right upper lobe.	Pneumonia and gangrene of right upper lobe. Acute fibrinous pleuritis.	98–101°	12,000	6 months	Dysphagia—6 months.	Colitis and peritonitis.
12 ♂ 46	Lower third	Right pleural cavity	Pleural effusion right side.	Empyema right pleural cavity.	99–101°	26,340	2 months	Pain in right chest.	Tuberculosis of pleura.
13 ♂ 52	Middle third	None	Cervical glandular enlargement.	Multiple metastases in lungs.	98	11,000	4 months	Cough and expectoration. Dyspnea. Swelling of neck.	Metastases to cervical and axillary lymph nodes, lungs.
14 ♂ 51	Middle third	None	Tracheal stenosis. Bilateral bronchopneumonia.	Bilateral bronchopneumonia.	102–104°	8,350	5 months	Dysphagia.	Recurrent laryngeal paralysis.
15 ♂ 42	Middle third	Mediastinum	No pulmonary signs.	Carcinoma of esophagus. Ulceration and perforation. Mediastinal abscess. Acute pericarditis.	None	10,000	6 months	Acute symptoms of mediastinitis one day. Dyspnea. Livid cyanosis of upper half of body.	
16 ♂ 58	Lower third	Upper third. Necrotic lymph node	Dyspnea. Tracheal obstruction. Fixation of trachea. Mediastinal tumor.	Carcinoma of esophagus with ulceration in lower third. Necrotic lymph nodes perforating esophagus and communicating with the right upper lobe.	99–103°	11,400	4 months	Weakness—14 weeks. Hoarseness—12 weeks. Loss of weight. Pain and cough.	Obstruction to esophagus in upper third due to lymph nodes—no obstruction at site of tumor.
17 ♂ 60	Middle third	Bifurcation of trachea		Tracheo-esophageal fistula. Pneumonia—R.L.L. R.M.L.	101–103°	9,000–13,700	7 months	Dysphagia—2 months. Anorexia—7 months. Cough and expectoration—1 month.	

The lesions responsible for the pulmonary and pleural signs are summarized in table 2, and the anatomical findings are listed in table 3.

TABLE II

Lesions Producing Pulmonary or Pleural Signs in 17 Cases of Carcinoma of the Esophagus

I. Tracheal and Bronchial Obstruction		2
1. Direct invasion of tumor	1	
2. Pressure and invasion of metastatic lymph node	1	
II. Perforation of Carcinoma		12
1. Trachea	4	
2. Right lung or pleura	3	
3. Left bronchus	2	
4. Left lung	2	
5. Mediastinum	1	
III. Necrotic Lymph Node Perforating Esophagus and Lung		1
IV. Aspiration of Infected Material into Bronchi		1
V. Multiple Pulmonary Metastases		1

TABLE III

Anatomical Findings in 17 Cases of Carcinoma of the Esophagus

I. Pleural Effusion		2
Left	2	
Empyema		2
Right	2	
II. Bilateral Bronchopneumonia		4
Unilateral Bronchopneumonia		2
III. Lung Abscess		
Left lower lobe	1	
Direct extension	1	
Left upper lobe	2	
Bronchial obstruction	1	
Direct extension	1	
Right lower lobe	3	
Direct extension	2	
Tracheal-broncho fistula	1	
Right upper lobe	2	
Aspiration	1	
Esophageal perforation from metastatic lymph node	1	
IV. Mediastinal Abscess		1
V. Pericarditis		1

Comment—General Features

All of the patients were men between the ages of 50 and 72 years. The primary lesion was located in the middle third of the esophagus in ten, in the lower third in five and in the upper third in two. The duration of the disease varied from two to nine months after the onset of the first symptom indicating disease. Once pulmonary or pleural signs became manifest there was fever varying from 98.6° to 103° F. or higher, and a leukocytosis between 9,000 and 32,000 per cubic millimeter. The symptoms and signs varied in accordance with the type of anatomical lesion and are discussed separately.

Perforation of Carcinoma of the Esophagus into the Trachea or Bronchi. In the group of cases reported here the trachea was perforated in four cases and the left bronchus in two. In all of them, the carcinoma arose in the

middle third of the esophagus. The symptoms and signs that developed following this complication were highly characteristic and consisted of *paroxysms of coughing and suffocation following the ingestion of fluid or food.* They were due to the passage of foreign material into the trachea or bronchi from the esophagus. After these symptoms and signs had been present for a varying period of time, evidences of pulmonary infection appeared, such as pneumonia or abscess formation. When the fistula was between the trachea and the esophagus the signs were either unilateral or bilateral; when there was a broncho-esophageal fistula the signs were unilateral, the side affected depending upon the bronchus perforated.

The details of an illustrative case of tracheo-esophageal fistula are recorded in case 1.

CASE I

A man, 60 years of age, was admitted to the hospital, complaining of difficulty in swallowing. Seven months before admission anorexia had begun, and two months before entry he noticed dysphagia and the regurgitation of solid food. This had increased until he could swallow only liquids. The examination at this time revealed evidence of loss of weight and a narrowing of the lumen of the esophagus at about the bifurcation of the trachea. Following a liquid diet and tincture of belladonna the patient's symptoms were relieved somewhat for about two months. Then the symptoms of dysphagia became worse and attacks of coughing developed following the ingestion of liquids. There was dull pain beneath the sternum which was increased by coughing. The cough was soon accompanied by the expectoration of dark-colored, foul-smelling sputum which was blood-tinged. For one week he had been hoarse. Examination at this time showed fever, emaciation, pallor, moderately enlarged lymph nodes in the supraclavicular fossae, fetor oris, impaired resonance and many fine râles over the right middle and right lower lobe, with bronchial breathing. Roentgen-ray examination showed infiltration of the lower half of the right lung. The white blood cell count was 10,000 per cubic millimeter. The sputum was foul-smelling and abundant, and there was moderate anemia. The clinical course was one of progressive failure, with high irregular fever, loss of weight and the signs of a diffuse suppurative pulmonary disease.

Necropsy showed a squamous cell carcinoma of the middle third of the esophagus which had perforated the trachea at the bifurcation, and pneumonia with abscess formation of the right middle and lower lobes.

Briefly, then, this case illustrates the sequence of events when a carcinoma perforates into the trachea at its bifurcation.

Inasmuch as carcinomata of the esophagus are most common in its upper and median third, it is not surprising that the trachea or bronchi are often invaded or perforated by the tumor. From general experience,[1, 2, 3] it is commoner to observe perforation of the trachea than of the bronchi, and when the latter are involved either one may be perforated. The left usually is perforated directly by the tumor mass, whereas the right is more often invaded by an abscess from the mediastinum which has resulted from perforation of the esophagus. In the cases collected by Zenker and Ziemssen [3] the right bronchus was involved more often than the left.

Perforation of the Carcinoma of the Esophagus into the Lungs or Pleural Cavities. The lungs or pleurae were the site of infection in five cases due to perforation of the esophagus and the direct extension of the infection into these structures. In four, the carcinoma arose in the lower third of the esophagus and the perforation caused right-sided empyema in one, abscess of the right lower lobe in two with empyema in one, and an abscess in the left lower lobe in another. In the remaining case, the upper third of the esophagus was perforated and the left upper lung lobe invaded. Aside from these cases in which perforation of the carcinoma was responsible for the pulmonary complication, a sterile pleural effusion was observed in two patients with a broncho-esophageal fistula and a bronchopneumonia.

From these cases, and others reported in the literature, the right lung or pleura is more often involved than the left when a carcinoma of the lower third of the esophagus perforates. The same is true when a pneumothorax occurs as a complication. The following case illustrates the course of events when the lung is invaded by a perforating carcinoma.

CASE VI

A man, aged 59 years, complained of "cough and stomach trouble." Nine months before admission he began to notice anorexia and a burning sensation in the lower part of the left side of his chest which came on soon after eating. Six months after the onset of symptoms he developed pain in the left side of the chest on respiration. The cough increased and was productive of large amounts of foul-smelling mucopurulent sputum. At the same time he noticed increasing difficulty in swallowing so that only liquids could be taken with ease and comfort. Upon examination, it was found that he had lost weight and coughed frequently. There was distinct clubbing of the fingers and pallor. Over the left lower lobe posteriorly there were dullness and râles. Roentgen-ray examination revealed slight cloudiness of the left lower lobe. The red blood cell count was 4,000,000 per cubic centimeter, the hemoglobin 65 per cent and the white blood cell count 22,000 per cubic millimeter. The sputum contained elastic tissue. High, irregular fever developed and the signs at the left lower lobe became more extensive with areas of solidification which were confirmed by further roentgen-ray examinations. The presence of a fistula between the esophagus and lung was established clinically by having the patient swallow capsules containing carmine, and then observing carmine in the sputum as long as three days later. The lesions progressed and the patient died. Necropsy showed a carcinoma of the lower third of the esophagus invading the left lung with abscess formation in the left lower lobe and metastases to the subdiaphragmatic lymph nodes.

This case illustrates, then, the results of a perforation of the lower third of the esophagus with an invasion of the left lower lobe, bronchopneumonia and multiple abscesses.

Tracheal or bronchial obstruction may arise as the result of a direct invasion of an esophageal tumor, or of a lymph node involved by a metastasis compressing either the trachea or bronchi. Three examples of these complications were observed. In all, the signs of tracheal or bronchial stenosis were present. In the case of tracheal obstruction, bilateral bronchopneumonia developed as a complication. In the patient with bronchial

obstruction, an abscess of the lung appeared. The following case is illustrative of tracheal stenosis resulting from an enlarged lymph node, containing tumor, in a patient with a carcinoma in the lower third of the esophagus.

Case XIV

A white man, 51 years of age, entered the hospital complaining that for the past four months food had repeatedly caught in his throat. The difficulty in swallowing had increased progressively but there had been no regurgitation of food. Upon examination, it was found that he had lost weight and was hoarse. There was paralysis of the left abductor muscle of the larynx, attributed to compression of the recurrent laryngeal nerve. Attacks of coughing coming on after the ingestion of large amounts of fluid may also have played a part in causing hoarseness. The trachea was fixed in the midline; the lungs were normal to physical and roentgen-ray examination. He had a moderate anemia, 3,770,000 red blood cells and 65 per cent hemoglobin, and a normal white blood cell count. Roentgen-ray examination showed a constriction of the esophagus in its middle third which was compatible with the diagnosis of carcinoma. He was treated by dilating the esophagus with bougies and obtained temporary relief from his dysphagia for approximately four months, when he began to have severe attacks of coughing and difficulty in breathing. These attacks followed the swallowing of liquids, and he frequently coughed up small particles of food.

At this time the examination showed an ill man who appeared prostrated and worn. There was obvious dyspnea with wheezing respiration suggesting tracheal obstruction. There was fever, cough, expectoration and hoarseness. There were no enlarged lymph nodes above the clavicle but there was fixation of the trachea to lateral movement, and it seemed to be displaced anteriorly. The lungs showed the signs of a bilateral bronchopneumonia. Otherwise the examination showed nothing remarkable. He failed rapidly and died nine months after the onset of symptoms. Necropsy showed a carcinoma of the middle third of the esophagus which had ulcerated but not perforated. There were large metastatic lymph nodes in the superior mediastinum which had produced recurrent laryngeal paralysis, tracheal and esophageal stenosis. There was a bilateral aspiration pneumonia.

In this case, then, there were two obstructive lesions of the esophagus, one at the site of the carcinoma, the other at the site of the enlarged lymph nodes in the superior mediastinum. The latter had produced, in addition, a stenosis of the trachea which was responsible for the physical signs and the bilateral bronchopneumonia.

In other cases, enlarged lymph nodes in the superior mediastinum, from carcinoma of the lower part of the esophagus, not only compress the esophagus as in case 14, but in addition they may cause perforations in such a manner that there is a communication between the esophagus and the lung. For instance, the following case.

Case XVI

A man, 58 years of age, complained of weakness and hoarseness of 14 weeks' duration. Accompanying these symptoms there was pain beneath the sternum, an unproductive cough, expectoration of small amounts of sputum, anorexia, progressive weakness and loss of weight. On examination there was hoarseness, stridor, cyanosis of the head with fullness of the neck. The larynx was prominent and fixed so that

it could not be moved laterally. The lungs showed signs of emphysema. There was paralysis of the right abductor muscle of the larynx, moderate increase in the retromanubrial dullness. The roentgen-ray examination showed a mass in the superior mediastinum. Fluoroscopic examination of the esophagus showed some delay in the passage of barium through the upper third of the esophagus.

Following roentgen-ray treatment over the mediastinum there was an increase in the cough with difficulty in swallowing, and the appearance of solidification and abscess formation in the right upper lobe, high irregular fever and leukocytosis.

Necropsy showed a non-obstructive carcinoma of the lower third of the esophagus. There were metastases in the lymph nodes of the mediastinum and these had invaded the esophagus, the trachea and the lung, and had produced a fistula between the eroded esophagus and the upper lobe of the right lung.

This case illustrates that lymph nodes with metastases not only produce obstruction but that they may cause perforation of the esophagus and fistulous communications.

When the obstruction to the esophagus is in the upper third, the ingestion of food or fluid may be followed by an overflow from the esophagus into the trachea. This produces paroxysms of coughing, and may lead to aspiration lung abscesses, as in case 11.

In summary, then, pulmonary or pleural infections arise during the course of carcinoma of the esophagus by perforation of the growth into the lung, trachea, bronchi or pleura. An enlarged lymph node, due to metastatic tumor, may cause tracheal compression, or it may perforate both the esophagus and lung, producing a fistula. Finally, food may be aspirated into the trachea when there is obstruction.

Carcinoma of the Esophagus with Multiple Pulmonary Metastases. Rarely a carcinoma of the esophagus may remain latent and the manifestations become those of multiple tumor metastases in the lungs, as in the following case.

CASE XIV

A white man, 52 years of age, complained of irritation in his throat, which produced coughing without expectoration, of two months' duration. For six weeks he had had dyspnea on exertion, and a painless swelling on the left side of the neck in the supraclavicular region. Upon examination, it was found that he had lost a considerable amount of weight, and that there were masses of lymph nodes above the clavicles on both sides. The thyroid gland was irregular and nodular, there was increased retromanubrial dullness, but the heart and lungs were negative to physical examination. Roentgen-ray examination of the chest showed numerous round, dense areas characteristic of metastases to the lung. Roentgen-ray studies of the esophagus did not reveal any obstruction. Biopsy of a lymph node from the supraclavicular region revealed a metastatic carcinoma. The patient failed rapidly, and at necropsy a small non-obstructing carcinoma of the lower third of the esophagus with multiple metastases to the lungs and lymph nodes was found.

Differential Diagnosis. Two conditions which may be confused with carcinoma of the esophagus and its pulmonary complications are aneurysm of the aorta compressing and eroding the esophagus, and carcinoma of the

lung producing esophageal symptoms. The following two cases are examples.

Case XVIII

A man, 56 years of age, complained of difficulty in swallowing. Two months before admission he began to notice pain in the right side of the chest and dyspnea. These symptoms increased until one month before entry when he noticed dysphagia for solid food; this increased until it was impossible for him to swallow even liquids. He was well developed but had lost considerable weight. The examination of the chest revealed some dullness at the right base and the signs of a high right diaphragm. There were no signs of an aneurysm of the ascending, transverse or descending part of the arch of the aorta. The heart sounds were clear. Roentgen-ray examination of the chest showed a high right diaphragm with fibrosis of the right lower lobe of the lung. Due to the esophageal obstruction, a gastrostomy was done. Three days later there were signs of consolidation over the lower lobe of the right lung. A day later a to-and-fro friction rub appeared over the heart, and he died the same day.

Necropsy showed an aneurysm of the descending aorta which had ruptured into the mediastinum, forming a hematoma which had caused esophageal obstruction, necrosis and perforation of the esophageal wall and an abscess of both the mediastinum and right lung, and an acute pericarditis.

In this case the pulmonary signs resulted from a perforation of the esophagus due to erosion from a hematoma which arose from a ruptured aneurysm. The signs were predominantly esophageal and pulmonary.

In the following case, the carcinoma arose in the lung and invaded the esophagus causing necrosis and perforation.

Case XIX

A white man, 80 years of age, complained of difficulty in swallowing. Four months before entry he began to have a severe distressing cough which was nonproductive in character. Three weeks before admission he developed dysphagia and was unable to swallow any solid foods, and for one week he had regurgitated both food and water. He had had pain in the left axillary region and back which was exaggerated by respiratory effort. There was progressive hoarseness and loss of weight. On examination he was found to be thin, emaciated and dehydrated. The trachea was deviated to the left and the left side of the chest moved only slightly during respiration. Over the left lower lung lobe there were physical signs of fluid, and above this area signs of solidification and of a fibrous pleurisy. The right lung was clear. The heart was displaced to the right but the sounds were clear. There was evidence of a paralysis of the inferior cervical sympathetic ganglion with a Horner's syndrome. There was a moderate anemia and a white blood cell count of 12,000. The pleural fluid was cloudy and contained many leukocytes and pneumococci type V. A gastrostomy was done on account of the dysphagia, and death followed one week later.

Necropsy showed a carcinoma of the left lung invading the mediastinum and esophagus with erosion of the latter, abscess formation in the lung and empyema of the left pleural cavity.

In this patient the esophagus was invaded and perforated by a tumor arising in the lung with resultant infection of both the left lung and pleura.

From the description of these cases, it is manifest that during the course

of a carcinoma of the esophagus a variety of pleural and pulmonary complications may arise which may imitate a large number of primary pleural or pulmonary disorders. In addition, there are a few extrinsic lesions of the esophagus that may produce not only esophageal but pulmonary symptoms and signs as well.

Summary

1. Seventeen cases of carcinoma of the esophagus are recorded in which pleural or pulmonary complications were the outstanding features of the disease.

2. Pleural and pulmonary complications of carcinoma of the esophagus result from perforation of the growth into the trachea, bronchi, lungs or pleurae, or as the result of obstruction of the air passages, of the aspiration of food, or of perforation of the lung by a necrotic metastasis in a lymph node.

3. The symptoms and signs caused by these complications may completely dominate the clinical picture and overshadow symptoms of the primary lesion.

4. The conditions that are to be discriminated from these complications are discussed.

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FURTHER OBSERVATIONS ON THE HEART IN MYXEDEMA *

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In a previous paper [1] we presented data dealing with changes in the size of the heart, in the blood pressure and in the electrocardiograms resulting from thyroid medication in myxedema patients. The most striking finding was a shrinkage in the transverse diameter of the heart of from 1 to 7 cm. in 20 of the 30 patients observed. Since then 18 additional patients have been studied. Forty-seven teleroentgenograms were obtained and measured. The method of study and the precautions taken were the same as those previously described.

Results

Table 1 summarizes the changes in the size of the heart and in the blood pressure of 18 myxedema patients as a result of treatment. Fifteen of the 18 patients had enlarged hearts, i.e. the transverse cardiac diameter was greater than half the internal diameter of the chest. The transverse diameter of the heart decreased in all but one instance, the decrease varying from 1.3 to 4.6 cm. The one patient, Mr. H. T., who failed to show a shrinkage in the size of the heart, had a normal sized heart before treatment, was suffering from angina pectoris and showed bundle branch block by electrocardiogram. He died suddenly at home a year later, probably as a result of coronary occlusion.

A few of the cases require special comment. The second teleroentgenogram in the case of Mrs. E. D. showed the diaphragm to be one and a half spaces higher than in the premedication plate, and in the case of Mrs. H. E., one space higher. Since a high diaphragm causes the cardiac measurements to be too large, it follows that the actual shrinkage of the heart in these two cases was greater than that observed. In the case of Mrs. J. N. the observed shrinkage was obtained after two weeks. Remeasurement of the heart five and one-half months later showed that the heart had returned to its original size. The reason for this probably lies in the hypertension persisting throughout this period. The patient, Mr. J. P., developed myxedema as a result of thyroidectomy for hyperthyroidism two months previously. The transverse diameter of his heart shrank after thyroid medication approximately to the size present before operation. This patient is exceptional in that he is the only one in either series who had rheumatic heart disease.

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From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital.

The various factors which may play a part in this cardiac shrinkage were discussed in the previous paper. The changes in blood pressure were of the same order as those in the previous series. Fourteen patients had electrocardiographic records made before treatment, and all of them showed some of the typical abnormalities found in myxedema. None of the patients showed evidence of congestive failure.

TABLE I

Change in Size of Heart and in Blood Pressure after Thyroid Medication in 18 Patients with Myxedema

Patient	Age	Basal Metab. Rate	Half Trans. Chest Diam.	Trans. Heart Diam. before Medication	Max. Heart Change after Medication	Time Interval for Change	Blood Pressure before Medication	Blood Pressure after Medication
			Cm.	Cm.	Cm.			
Mrs. E. W...	59	−30	13.2	18.9	4.6	11 mo.	190/120	208/112
Mrs. R. T...	55	−42	12.9	16.8	4.4	4½ mo.	125/90	
Mr. W. D...	48	−37	14.4	15.6	3.6	1½ mo.	120/80	110/72
Mrs. E. H...	36	−38	12.8	15.7	2.7	3½ mo.	88/64	106/68
Mrs. F. B...	57	−41	12.3	15.5	2.5	2 mo.	130/80	120/56
Mrs. C. E...	60	−23	12.3	14.5	2.0	7½ mo.	170/100	128/66
Mrs. L. D...	47	−46	13.1	14.6	2.0	1 yr.	110/65	142/90
Mr. W. A. ..	18	−45	12.6	11.5	1.9	2 wk.	105/78	
Mrs. H. E...	39	−40	13.8	15.0	1.7	5 wk.	140/100	136/84
Mr. P. M. ..	55	−33	15.0	15.7	1.6	1 mo.	112/72	116/62
Mrs. J. N. ..	67	−33	12.5	16.1	1.6	2 wk.	195/110	180/95
Mr. J. P. ...	16	−44	13.3	14.6	1.6	9 mo.	114/90	120/86
Mrs. M. T...	42	−44	12.6	13.6	1.6	8 mo.	170/108	114/62
Mrs. E. D...	46	−35	13.7	16.3	1.5	6 mo.	165/104	130/90
Mrs. N. P...	44	−39	12.8	11.8	1.5	6 wk.	110/84	100/56
Mrs. A. L. ..	46	−44	12.3	14.1	1.3	11 da.	110/80	104/66
Mrs. H. S. ..	55	−27	12.5	15.1	1.3	14 mo.	170/110	216/128
Mr. H. T....	55	−29	13.8	13.1	−0.4	3 mo.	130/98	130/80

In our previous paper we mentioned the pathological changes in the hearts of five patients, examined post mortem, two of whom had not received any thyroid medication. Recently, we had the opportunity, through the kindness of Dr. J. H. Townsend, to see a patient with myxedema, who died before treatment could be instituted. The heart in this case * was hypertrophied and the myocardium soft and friable. Histologically the muscle bundles and fibers and the connective tissue were widely separated by interstitial edema.

Two papers on this subject which appeared recently are worthy of mention. Hallock [2] reported two patients with myxedema, one showing gross congestive failure which disappeared under thyroid medication, and the other showing a diffusely dilated heart and a subnormal minute volume output, but no gross cardiac failure. No question can be made of the

* We are indebted to Drs. H. E. McMahon and R. Osgood, for permission to mention the cardiac findings here. They will publish a complete pathological study of this case in the near future.

facts presented by this author, but we cannot agree that a diffusely dilated heart, accompanied by signs of dyspnea, or a decreased minute volume output are evidence of cardiac failure. We believe, rather, that they are part of the picture of myxedema. The paper of Ohler and Abramson [3] concerns itself mostly with the electrocardiographic changes in myxedema. Thirteen of their 21 patients studied showed abnormal electrocardiograms. Cardiac enlargement occurred in seven of the patients with abnormal electrocardiograms, and in all but one the size of the heart diminished under thyroid therapy. However, their data do not warrant the conclusion that mild congestive failure is a frequent clinical finding. It is also difficult to explain why they get electrocardiographic abnormalities in only 62 per cent of their cases, whereas we get abnormalities in all of our cases.

Summary

The changes in the size of the heart and in the blood pressure of 18 patients with myxedema under thyroid medication are presented to supplement the data of 30 patients previously reported. It appears to be characteristic of the heart in myxedema to be enlarged and to undergo appreciable shrinkage as the disease is ameliorated by the administration of thyroid substance. All of the electrocardiograms of these patients taken before treatment showed abnormalities. None of the patients showed congestive failure.

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SMALL INTESTINAL INTUBATION: EXPERIENCES WITH A DOUBLE-LUMENED TUBE *

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Introduction

The small bowel, excepting the duodenum, has been less extensively and less satisfactorily studied than any other unit of the gastrointestinal system. Various explanations readily suggest themselves: its inaccessibility for direct investigation; the complexity and varied sources of its secretions; the difficulty of obtaining its contents, even in experimental animals, in a normal state of the organ; its elusiveness under the roentgen-ray; its relative immunity from disease. Our knowledge of its secretory and motor functions has rested almost entirely on animal experimentation, on chance observations at operation and on the study of the contents obtained after jejunostomies and ileostomies, methods which, nevertheless, have led to invaluable results.

Several workers [1, 2, 3] have accomplished small intestinal intubation in man; McClendon and his associates,[2] in 1920, reported on the hydrogen ion concentration of the contents aspirated from two subjects, but their technic required four days for the tube to reach a level at most four or five feet below the pylorus. None of their methods has led to extensive investigation or important results. Recently, however, we [4] have developed a technic that seems practical, and that, we believe, may eventually be applied in a more or less routine fashion.

Principles of the Technic

The passage of the tube along the bowel depends upon the attachment to its distal end of a collapsible rubber balloon which, when distended in the third portion of the duodenum, stimulates peristaltic waves that carry it down the intestinal tract (figure 1). The injection of substances into, and the aspiration of material from, the bowel is provided for by having the tube double-lumened: one lumen for distension and deflation of the balloon; the other, for injection and aspiration.

The tube may be introduced into the duodenum in the usual way or by manipulation under the fluoroscope according to Morgenstern's [5] technic. By the latter procedure we have sometimes been able to have it enter the jejunum within three to five minutes. When the balloon, in the duodenum, is moderately distended with air under the fluoroscope it usually can be seen to rush immediately to the region of Treitz's ligament. Some massage over

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From the Gastro-Intestinal Section of the Medical Clinic, Hospital of the University of Pennsylvania.
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that point commonly causes it to move slowly around the curve into the jejunum and then to rush 20 to 30 cm. farther very quickly. Once the jejunum has been entered, we have found it practicable to allow the patient considerable freedom so long as he continues to swallow the tube at the rate of one centimeter per minute until its proximal end has nearly reached the mouth. At that time he should be re-fluoroscoped to make certain that no coiling of the tube in the stomach has taken place (figure 1).

The outside diameter of the tube is only 6 mm., but each lumen is slightly larger than that of the ordinary duodenal tube; the length which we have

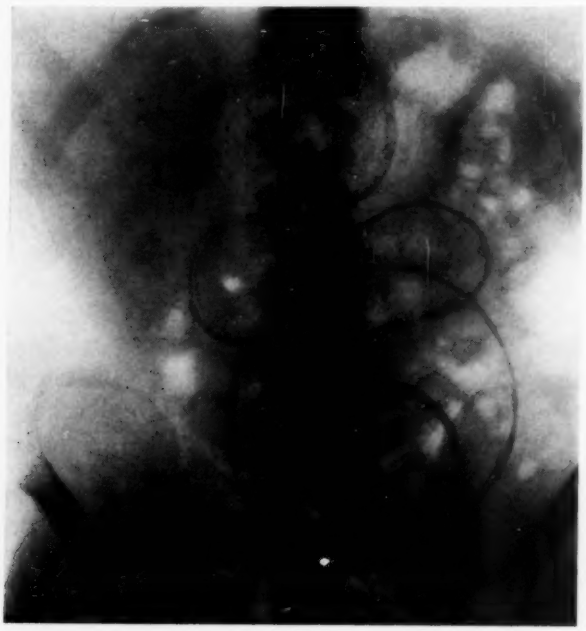

FIG. 1. Roentgenogram showing double-lumened tube with attached balloon in small intestine. Note characteristic curves of parts of tube in stomach and duodenum. One lumen of tube filled with 8 per cent sodium iodide solution; balloon partly filled with iodide solution, partly with air.

found suitable for reaching the ileum is nine to ten feet (270 to 300 cm.), this allowing the tip easily to advance five to six feet (150 to 180 cm.) beyond the pylorus. In one instance with only this length of tubing the balloon reached the middle of the transverse colon (figure 2). Only in that case did we have a balloon pass beyond the terminal ileum; yet when it passed as much as four or five feet below the pylorus it was always beyond the jejunum, because when a barium mixture then was injected no valvulae conniventes could be seen. Such intubation of the intestines has often required not more than three hours, and being accomplished in the morning has allowed the afternoon for experimental procedures.

We have introduced the tube into the small intestine for a distance of 100 cm. or more in 75 persons, doing in all more than 100 intubations. At first we failed in about 50 per cent of the attempts, due chiefly to inability to traverse the pylorus within a reasonable time, but, since using the Morgenstern technic, have been successful in fully 80 per cent. In no instance, with the balloon deflated, have we had any difficulty in removing the tube by mouth. Some of the subjects have been ward or out-patients; others, unemployed individuals to whom we paid small fees.

FIG. 2. Roentgenogram showing double-lumened tube in stomach, duodenum, small intestine and large intestine to middle of transverse colon. Barium solution was introduced by tube after tip had reached the transverse colon, and none of barium appears in small bowel.

In making the aspirations the following method has been employed routinely: with the distal end of the tube at the desired level in the bowel, determined by the length of tubing swallowed and by fluoroscopic observation, the balloon is deflated, or it is allowed to remain only slightly distended in order to interfere with the escape of contents beyond the orifices of the collecting lumen. The proximal end of the aspiration lumen is connected with a syphon drainage system arranged to maintain constantly a negative pressure of 60 cm. of water and to allow the collections to be made, under oil, into glass receptacles that may be changed as desired (figure 3).

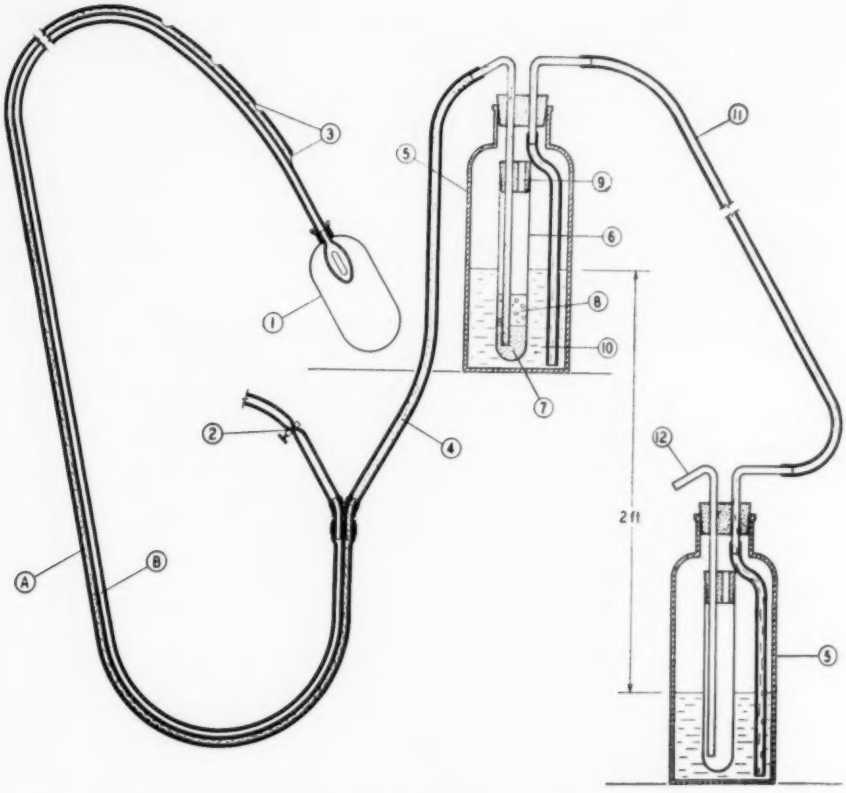

FIG. 3. Longitudinal section of double-lumened intestinal tube with attachment to system for making collection of intestinal contents. *A* indicates lumen used for aspiration; *B*, lumen for inflation and deflation of balloon (1); *2*, clamp on proximal tube connected with *B*; *3*, perforations; *4*, proximal tube connecting *A* with collecting system; *5*, bottles partially filled with water (*10*) and connected by tube (*11*) so as to maintain constant negative pressure; *6*, glass tube for collection of specimen; *7*, specimen; *8*, oil, originally injected into *4* and *A*, and now overlying specimen; *9*, doubly perforated stopper.

EXPERIMENTAL OBSERVATIONS AND COMMENTS

The fasting intestinal contents, under the conditions of the method, have come out in small spurts, often of only a few drops, sometimes a few cubic centimeters, with irregular intervals of minutes when no flow occurred. This has suggested the influence of peristaltic waves or of changes in the tonus of the intestinal walls bringing down the bowel small amounts of secretion at a time. Occasionally much larger amounts, 10 to 20 c.c., have come through the tube in a continuous rapid flow: this, as demonstrated by introducing a dye into the stomach, has resulted from an unusually rapid passage of gastric contents to the balloon area. Under such circumstances the material collected has been more liquid, lighter in color and of a lower hydrogen ion concentration. Ordinarily the material collected under fasting conditions had the gross characteristics of duodenal fluid, being slightly cloudy, usually of a light yellowish or greenish color, sometimes dark green,

and changing after standing to a perfectly clear solution with a slight, semi-mucoid sediment. Occasionally, but only in achlorhydric individuals with a nasal discharge, small shreds of mucus with pus cells embedded in them have been encountered, but never of sufficient quantity to occlude the tube lumen. This would suggest that the presence of the tube does not lead to irritation of the bowel wall.

Under fasting conditions, with the balloon empty or moderately deflated, it sometimes required one to two hours to secure a specimen of 5 to 15 c.c. of material, and in 13 cases an average of only 33 c.c. per hour was obtained. Whether under such conditions very little gastric, duodenal and jejunal secretion occurs and little biliary and pancreatic secretion is ejected from the common bile duct or whether the secretions are largely absorbed as they pass down the jejunum and ileum has not been determined: doubtless both are factors in varying relationship.

In six subjects, when 150 to 450 c.c. of water had been administered by mouth while the tube was being swallowed, some of them taking most of it during the hour preceding the first collection, the average rate of flow through the tube was actually decreased to 22 c.c. per hour. Nevertheless, the chloride content in the specimens after the administration of water by mouth was often reduced, indicating that some dilution, probably with proportionate increase of absorption, had occurred. When to one subject 2 gm. of decholin were given intravenously, no increase of flow was observed. When 0.5 c.c. of a 1 : 1000 solution of histamine was given subcutaneously to each of 10 cases no increase in the rate of flow occurred until the gastric secretion that followed the histamine injection reached the area from which the collection was being made, indicated by the presence in the specimen of vital red, which had been introduced into the stomach at the same time that the histamine was injected. Thereafter the average rate of flow was increased to 64 c.c. per hour. Also, in several instances, 100 c.c. of a 25 per cent glucose solution had no effect on the rate of flow until the sugar itself appeared in the specimen; then the average rate of flow was 82 c.c. per hour.

These observations seem to indicate that the normal content of the small bowel at or beyond the jejuno-ileal junction under fasting conditions is small in amount and that it passes down the tract at a relatively slow rate; that the administration of histamine subcutaneously has little, if any, immediate effect on the volume of the intestinal content, but that eventually, when the gastric secretion of higher acidity that follows the histamine reaches the drained area, a moderate increase in the amount and rate of flow of the intestinal contents occurs; and that a hypertonic glucose solution introduced orally produces a more marked increase in flow, but again only when the solution itself reaches the area of bowel under investigation.

The ultimate increase in the amount of contents after histamine and glucose is undoubtedly due, in part at least, to the added increment from the stomach; but also, since the acidity usually was not appreciably lowered, it is obvious that there occurs, in addition, an increased flow of alkaline material

from the pancreas and perhaps the liver. Although certain animal experiments recently performed in the Surgical Research Department of this University show that after histamine an increase of succus entericus develops in closed intestinal loops, the failure of an increased flow in our human cases until the gastric contents arrived would suggest that the increased flow of intestinal secretion is due to altered chemical conditions in the upper small intestine rather than to a direct action of the histamine.

An extensive study of the chemical nature of the small intestinal contents at various levels and under various conditions is being made in this Clinic by Abbott and Karr, and will be reported upon later. It may be said here, however, that, using a quinhydrone electrode, the hydrogen ion concentration has been found in the neutral range (pH 6.6 to 7.3), whether pure fasting contents or material collected after the administration of histamine subcutaneously, decholin intravenously, or glucose or fats by mouth were studied. This is in agreement with the work of Mann and Bollman [6] and of others on animals. The intestinal fluid maintains its tonicity with blood plasma under most experimental conditions, but it may apparently under certain special circumstances become hyper- or hypotonic temporarily. The tonicity is maintained primarily, according to Abbott and Karr's results, by a balance between the chlorine and carbonic acid anions. The fasting calcium and phosphorus are usually within the blood plasma range.

In regard to the motor function of the intestine Abbott has been able, by connecting the intestinal balloon to a recording apparatus, to secure tracings from the small bowel, and on one occasion from the colon, that indicate changes in pressure incident to the exhibition of certain drugs quite as successfully as they have been obtained in dogs with intestinal fistulae. Thus he has demonstrated nitrite inhibition of intestinal movements, the slower but more prolonged suppression of activity by atropine (figure 4), the increase of peristaltic activity following posterior pituitary extract and the effects of other drugs such as physostigmin and acetyl B methylcholin.

By removing the lateral wall from one lumen of the double tube for a certain distance above its distal end and attaching to the shortened lumen a second balloon it has been possible to secure simultaneous kymographic records from two known sections of the tract. Thus one balloon may be in the stomach or duodenum and the other in the jejunum or ileum at any desired distance from the pylorus.

Furthermore, it has been found practicable to give a subject a small barium meal and so to visualize the stomach and intestine while at the same time making kymographic records. In this way Abbott and Pendergrass have been able to show the effect of peristaltic activity, as recorded, on the intestinal contents, to separate increase in tonus from peristalsis, and to indicate the direction, whether upward or downward, of any particular peristaltic

wave. Specifically, by this combined technic they have demonstrated that the gastric retention which follows the exhibition of morphine in man is due to an increased tonus of the muscular wall reaching its greatest intensity not in the pylorus but in the duodenum. On several occasions they have observed the barium mixture advance farther than the cap, while a balloon in the portion of the duodenum through which barium was not passing was re-

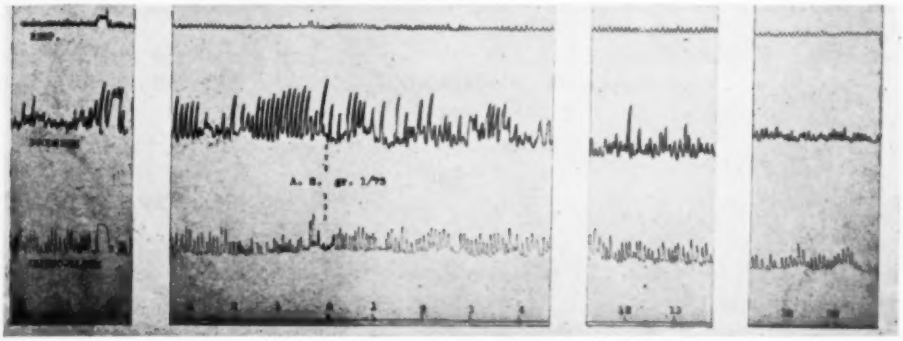

FIG. 4. Simultaneous tracings of respiratory rhythm and of duodenal and ileal contractions in a healthy intact human subject. Balloons in duodenum and in ileum were attached respectively to the two lumina of double tube, and the ileal balloon was 160 cm. below the pylorus. Note inhibitory effect of 1/75th gr. of atropine, injected subcutaneously, on the duodenum, and its less marked effect on the ileum.

cording a prolonged spasmodic contraction. They have been enabled by the kymographic records to determine when the enlargement of a segment of small bowel, as seen under the fluoroscope, is due to relaxation of tone and when it is due to forced distention by the passage down the bowel of intestinal contents. By omitting the second or proximal balloon and by making continuous suction well above the balloon, they have studied the pressure changes in a segment of bowel independent of any contents coming down from above.

CONCLUSION

Thus, we have referred to various experiences with a new method of studying the secretory and motor functions of the human small intestine to indicate the value of the technic, and have presented certain data that confirm results obtained previously only by animal experimentation. It is believed that further experience will lead to simplification of the technic, making it available eventually for the study of pathologic conditions of the small bowel.

We are indebted to Dr. W. G. Karr, Chemist to this Clinic and Assistant Professor of Physiological Chemistry in this University, for the chemical examinations reported upon in this communication.

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DIAGNOSIS AND TREATMENT OF CERTAIN TYPES OF CHRONIC DIARRHEA*

By PHILIP W. BROWN, M.D., F.A.C.P., *Rochester, Minnesota*

IN fully two-thirds of the cases of chronic diarrhea encountered at The Mayo Clinic there are no definite findings to explain the trouble. These patients usually have drifted from one place to another, have followed dietary fads, and have had the colon flushed. They constitute a puzzling group for both diagnosis and treatment.

There is a so-called harmless type of diarrhea which does not impair the patient's health; this may be present for years and the weight may be normal or even above normal; anemia is not present, and other laboratory studies give negative results. This type may be thought of as the "habit of diarrhea," similar to the "habit of constipation." It should be cared for on a sane, causal basis, and seldom necessitates medication. Of the number of people who lack free hydrochloric acid, it is surprising how few have diarrhea; even more surprising is the small percentage of those who receive benefit by taking acid.

The most common type of chronic diarrhea is that due to neurogenic or psychogenic factors; even in other types, the diarrhea seems to have its origin in shock or nervous upset. A lawyer may have a "running of the bowels" prior to a court trial, and a high-strung, nervous person may have diarrhea when under any emotional strain.

The term "colitis" is especially harmful when applied to this group; it is interesting and amusing to read of colitis as referred to in "The Story of San Michele," but it is another matter to treat patients after they have become obsessed with the idea of colitis. They search for the colitis specialist, the colitis serum, and the colitis diet. Certainly the term colitis should be reserved for cases in which inflammation of the colon is actually present. Some of these nervous people have diarrhea and constipation alternately. The relationship between irregularity of the bowel and nervous strain may not be as apparent as in the purely nervous group of patients. The patients should be instructed and educated in habits of living and eating, but should not be treated for colitis. Wholesome, simple meals, without excessive roughage, and a sane balance between work and play is the ideal program. Seldom is it fully realized, but much more is accomplished by striving for it than by irrigating, vaccinating, or dieting. The judicious use of mild sedatives is practically the only medication that should be considered. "Treat the patient, not the colon" would seem a wise motto.

It is obvious that the treatment of such cases must never be undertaken until all possible causes for the dysfunction of the bowels have been investigated. No matter how neurotic and hysterical the patient may be, the fail-

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ure to recognize early carcinoma of the bowel, chronic ulcerative colitis, or hyperthyroidism will react most unfavorably on any physician who has diagnosed the trouble as "nervous." Such errors must occur occasionally, but no effort should be spared to rule out organic disease.

I have reviewed the records of about 700 patients who have been examined in the past four years and whose condition was diagnosed as diarrhea of uncertain origin. Many had acute intercurrent enterocolitis. Psychogenic and neurogenic types of diarrhea were most common among the chronic cases. But, in addition, three other, smaller but definite groups were observed. In one group the condition seemed related to allergic phenomena; in one it was a sequel of an acute infection, and in the third the diarrhea was a prominent symptom of a deficiency disease (table 1).

TABLE I

Chronic Diarrhea

	Allergic (34 cases)	Postinfectous (24 cases)	Deficiency (20 cases)
Etiology			
Incidence by sex	Equal	Equal	Females to males; 4 to 1
Onset	Early life, after emotional stress	Following any acute infection	Insidious, dietary deficiency
Allergy (hives, hay fever and so forth)	Frequent	No	Occasionally
Symptoms			
Type of diarrhea	Sudden attacks or explosions	Steady or intermittent, watery	Large, bulky, gray, foul
General condition	Good	Good to fair	Fair to poor
Stomatitis, vaginitis, tetany	No	No	Common
Anemia	No	Seldom	Common
Treatment			
Diet	Adequate, elimination diets, keep a food diary	Adequate, low residue	High vitamin, high protein, low residue
Drugs	Soricin, calcium, sedatives	Iodine, dihydranol, vaccine calcium	Liver extract, calcium, parathyroid, iron

ALLERGIC DIARRHEA

In bringing up the subject of allergy, one immediately invites criticism. The enthusiast labels most of the cases of nervous diarrhea as allergic in cause, whereas those at the other extreme refuse to consider allergy unless the patient has a violent and prompt reaction following ingestion of a certain food. Too much stress can be laid on allergic reactions, but when I re-

viewed this large group of patients with diarrhea, I noted that some patients had an inherent peculiarity which might contribute to the dysfunction of the bowel. Skin tests for sensitivity have not yet proved to be as valuable for ingested as for air borne substances, although the number of positive reactions to foods is increased by use of the intradermal method. Interpretation of results is difficult, partly because all allergic persons are high strung and emotional, although the reverse is not true. Again, it is puzzling to find that people become intolerant to foods formerly well tolerated. Perhaps acute infection or nervous depletion may antedate the explosion of what has been latent allergy. Some people begin to have hay fever in middle life, although they have lived in the same community for years.

I selected only 34 cases for study, because the data on them were adequate, and usually further information had been obtained. During the past four years, economic stress has made it difficult for many patients to remain away from their work for observation and treatment. What follows is based on these 34 cases although some of the statements are general and in the present tense.

In this small group of cases numbers of males and females were equal, and the average age was the late thirties. Most of the patients were aware of peculiar reactions, either hives, hay fever, or digestive upsets since early adult life, whereas nine of them stated they had always suffered from disorders which a physician would interpret as probably allergic. Twenty of the group had had the following allergic phenomena for five or more years: nine had migraine; five, urticaria; one, asthma, and five, hay fever. Allergy in the family was noted only in six cases. Six patients had probable allergic manifestations for one year or less; in four of these, fatigue, acute intercurrent infections, or mental stress seemed to have been precipitating factors.

That the condition may be allergic diarrhea is suggested by the history of rather sudden attacks of loose bowel movements which occur either during the day or at night. A third of the patients normally had loose bowel movements, with occasional attacks of diarrhea. The remainder of the group had the sudden, acute attacks that would last from an hour to several days. The foods which the patients considered factors in producing trouble were chocolate, clams, veal, pork, various fresh fruits and vegetables, and fats. Milk was a known offender in five cases. Two patients were sensitive to iron and belladonna. A patient may state: "Both my boys and I are scoured by veal and pork." Often the evidence for allergy must be inferred. If the general examination gives negative results, if the patient's weight and color are good, and if direct or indirect evidence of allergic reactions is present, the diagnosis is suggested. Some patients, either on their own initiative or on advice, have eliminated so many foods that they have lost weight and perhaps even have developed some deficiency. This may cause confusion, and caution must be exercised whenever a diet is prescribed.

Treatment. This may be both specific and nonspecific. The former refers to omission of the offending foods from the diet. Often, these foods

are not known, and yet a physician dislikes to make a diagnosis of "just nervous diarrhea." It is hard to say why calcium helps some patients. Perhaps an excess supply of it may replace that lost in the stool, or again it may have a definite influence on the metabolism of muscle and nerve tissue. To influence the level of the blood calcium, it must be administered with the patient fasting. I prescribe one heaping teaspoonful of calcium lactate or tribasic calcium phosphate in warm water three hours after meals, or two teaspoonfuls on arising and on retiring. Morris and Dorst's suggestion of soricin (purified sodium ricinoleate) has been followed in several cases, that is, prescribing a globule of 10 grains (0.65 gm.) to be taken with cold water half an hour before meals. It is still not understood by me what soricin accomplishes, and yet with its use alone or in combination with the calcium I have had gratifying results in several instances. Seven patients have been greatly benefited by this regimen, whereas four others felt that the soricin was of no value. Various regimens, such as calcium with soricin, with parathyroid given orally, with dihydranol, or with sedatives have proved beneficial to 13 patients, whereas the condition of six others was not improved. In all instances, an effort was made to see that the diet was sufficient in all food elements. Occasionally, elimination diets, as first suggested by Alvarez, and later carefully worked out by Rowe, were advised but lack of time and funds usually necessitated the patients' following this plan at home. Vaughan recommended keeping a food diary; this is particularly valuable if the patient is intelligent and not too neurotic. Vaughan stressed that the patient must not note just "cheese or salad eaten," but what kind of cheese, the components of the salad, and the kind of oil used in the dressing.

Measures to improve the general physical and nervous stability are as important as drugs and diets. Recreation, work, stimulants, and frequently oral foci must be thoroughly considered. In two cases, the apparent intolerance to certain foods with associated diarrhea was greatly benefited by elevation of the low metabolic rate; soricin also was administered. Both patients insisted that occasional courses of soricin, added to maintenance of the metabolic rate at about minus 5 per cent, were essential to their good health.

Postinfectious Type of Diarrhea

This term is applied to a group of cases in which diarrhea, either steady or intermittent, is a sequel of an acute infection; this may have been appendicitis with rupture, "intestinal flu," or "food poisoning." The actual initial infection is not always definite, and yet I was impressed by the records of 24 cases in which some acute episode had been followed by dysfunction of the bowel. These 24 patients had had diarrhea from three months to 15 years, with an average of about two years. Eleven of them had attacks of diarrhea, whereas 13 had more or less constant looseness of the bowels. Six of them had lost a little weight. Six had moderate secondary anemia; the patient with the anemia of lowest grade had 9.5 gm. of hemoglobin per 100 c.c. of blood. Patients of this group were more definitely

disabled than those of the allergic type. As a rule, the degree of anemia or loss of weight was proportionate to the dietary regimens which had been followed.

Treatment. In view of the onset with infection, cultures of stools were made in nine instances, although there was no thought of identifying any organism which initiated the diarrhea months or years previously. Effort was directed toward obtaining the organisms which predominated and preparing a vaccine, as suggested by Dorst and Morris. Five patients considered that much benefit resulted, while four patients were not improved. Three patients were markedly improved following removal of infected tonsils or devitalized teeth. Removal of definite oral foci is always justifiable in any cases in which the cause of the diarrhea is indeterminable, although one should be conservative in promising definite results. Following the use of drugs, success has been none too good. Dihydranol, calcium, sedatives, soricin, parathyroid tablets, tincture of iodine, and inert powders are among the chief drugs that have proved helpful in different cases. One patient may be benefited by iodine, another may not, but is benefited by dihydranol, and so on. I tell such patients that a satisfactory regimen is usually evolved, but that I cannot plan, in advance, the individual program. Even more than in the cases of allergy, the personal and painstaking supervision of the patient is essential to obtain a good result. Seventeen of 24 patients stated months later that their condition was good, whereas the remainder were no better. Among the failures, I was impressed by the associated marked nervous exhaustion and occasionally psychosis. I still do not think that the unstable nervous system is the main factor in these seven cases, but, as in other diseases, it is most important. Interestingly enough, five of these seven patients stated that their general health was now good although the diarrhea persisted; perhaps the "habit of diarrhea" had become established.

Deficiency Diarrhea

I think of this more as a syndrome, rather than a disease entity and of the diarrhea as one of the symptoms. It may be an involuntary type of deficiency as in nontropical sprue, or the voluntary type in which the patient has curtailed his food. If the patient becomes enmeshed in bizarre eating notions, such as faddist diets for ulcer, for diabetes, for colitis, or for purposes of reduction in weight, any of the previously named types of diarrhea may develop into deficiency diarrhea. I have seen severe states of depletion, with marked anemia, great loss of weight, diarrhea, and occasionally edema, which have developed from what seemed originally to be a nervous condition. Certainly it is a nervous diarrhea, but the patient eventually becomes seriously ill. Whether these syndromes of depletion are due to low intake of protein, or to loss of vitamin B, or to some other unrecognized factor, I am uncertain. I am not including cases of celiac disease or idiopathic steatorrhea.

In this group of cases of deficiency diarrhea, there were 20 patients, 16 of whom were women. In the other groups, the sexes were about equally involved. This is too small a group to permit any conclusion, but the preponderance of women is of interest. The average age was in the thirties, and the average duration of intestinal symptoms was about five years. The onset was insidious in half and abrupt in the remainder. Three patients had lost but little weight, whereas 17 had lost from 5 to 60 pounds (2.3 to 27.2 kg.). Stomatitis, glossitis, and vaginitis occurred singly or in combination in 10 cases. The stools were watery, often large and bulky, grayish, and occasionally frothy. Cramping of the extremities was present in two cases; in one, it was severe enough to necessitate hospitalization and prompt intravenous injection of calcium. Analysis of gastric contents of four patients revealed no free acid, but administration of hydrochloric acid was of no value.

Secondary anemia was present as a rule. The average value for hemoglobin was about 11 to 12 gm. per 100 c.c. of blood, although it was as low as 5.4 gm. in one case. The erythrocyte count was lowered, with a tendency to a high color index. The leukocyte count tended to be low; the highest count in all the cases was 8,500, while in the majority of cases it was about 5,000. In two cases, in which tetany and edema were associated, the value for calcium was 5.6 and 7.0 mg. per 100 c.c. of blood; the plasma proteins were 4.3 mg. and 4.1 mg. per 100 c.c. of blood.

Treatment. I think success varies directly with the coöperation of the patient and the opportunity to follow each case. Individual treatment is imperative. Of these 20 patients, 12 later reported that they were well; five were improved, and the condition of three was unchanged. In three cases, vaccines from cultures of the stool were tried, were found helpful in one case and were of no value in two others. Calcium was beneficial in 11 cases. In four cases, calcium and parathyroid extract were effective. More recently in the severe cases, especially if anemia was marked, intramuscular injections of liver extract in conjunction with large doses of iron have proved of value. If ferric citrate increased the diarrhea, 4 to 6 gm. daily of Blaud's mass or 3 gm. of reduced iron usually would be tolerated. Foreign protein in the form of intravenous injections of typhoid vaccine was of no value in one case. If depletion and exhaustion were severe, transfusions of blood speeded the convalescence. A diet high in vitamins, high in protein, and yet with minimal residue was instituted. On each tray would be two tablets of Harris' yeast, and 20 to 30 drops of haliver oil with viosterol, or 1 ounce (30 c.c.) of cod liver oil was given each day. Many of the patients were given anti-amebic treatment, either to ensure that amebic infection was not overlooked, or as nonspecific treatment. No benefit ensued from the use of these drugs.

Relapses are not uncommon. The patient must adhere to this general program for an indefinite period. Nervous shock or acute infection may

precipitate a relapse. The margin of safety of these patients is low, and they need more protection than the average patient.

Conclusions

1. The diagnosis of colitis should be reserved for cases in which actual inflammation is demonstrable.
2. Neurogenic and irritable intestinal syndromes constitute the largest group of cases of chronic diarrhea.
3. Certain persons have inherent peculiar reactions which probably produce or increase intestinal function. This is called allergic diarrhea.
4. Following any acute infection, diarrhea may develop and persist for months or years.
5. As a result of voluntary or involuntary curtailment or omission of certain foods, a deficiency syndrome may result, with diarrhea a prominent symptom.
6. Experiences in treatment of the patients in the foregoing groups have been recorded.
7. These clinical experiences reveal the need of much investigation by the biochemist, the bacteriologist, and the physician.

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3. Vaughan, W. T.: Food allergens; trial diets in elimination of allergenic foods, Jr. Immunol., 1931, xx, 313–332.

EDITORIALS

RELAPSING FEVER IN CANADA

In 1933 Palmer and Crawford[1] reported six cases of relapsing fever which occurred in the summers of 1930, 1931 and 1932 in the Arrow Lake region of British Columbia. In two of these cases spirochetes were found in the peripheral blood. This constitutes the first report of the occurrence of relapsing fever in Canada.

In the United States the disease has been so seldom recognized in the last fifty years that to most physicians it is little more than a name recalled from student days. Knowing, as we do, that epidemics of the disease have always been associated with times of war and famine, we have perhaps been scarcely grateful enough that it played no part in the mortality from disease in our Army in the World War and that through these recent years of depression it has not broken out among our millions of destitute citizens. Yet it is far from being an extinct disease. It is endemic and at times epidemic in European Russia, Poland, Finland and the Balkan States. In Serbia there are said to have been more than 12,000 cases in the World War. It is prevalent throughout a large part of Africa. The Belgian troops in East Africa in the War suffered heavily. Outbreaks and sporadic cases occur in India, China, Manchuria, and the Dutch East Indies. Nearer home, foci of the disease have been found in Columbia, Venezuela, Panama, and Mexico. In the United States, however, Palmer and Crawford were able to find record of less than 20 reported cases since 1875.

Prior to 1875 the Eastern seaboard was subject to a number of outbreaks of relapsing fever. During the decade from 1842 to 1852 the disease was very prevalent in Ireland, Scotland and England. In June 1844 an emigrant ship from Liverpool landed 18 cases of relapsing fever in Philadelphia. Fifteen of these were studied by Clymer and described in his book on fevers. Similar emigrant groups ill with the disease were seen in New York in 1848 and 1850 and in Buffalo in 1850. In 1869, 1870 and 1871 occurred the only widespread American epidemic. The disease was very prevalent then in New York, and Austin Flint studied over 100 cases on the wards of Bellevue Hospital. In Philadelphia there were over 1,000 cases and scattered cases were seen in the City of Washington and in Maryland, New Jersey and Connecticut.

Though with our present knowledge of the mode of transmission of the disease we should now be in a position to defend our population against similar great epidemics, it cannot be said that it is yet clear why we have been spared further outbreaks since that of 1870.

The first advance in our knowledge concerning the etiology of the disease

[1] Palmer, J. H., and Crawford, D. J. M.: Relapsing fever in North America, with report of an outbreak in British Columbia, Canad. Med. Assoc. Jr., 1933, xxviii, 643–647.

came in connection with the epidemic in Continental Europe which preceded and accompanied the American epidemic. In 1868 Otto Obermeier,[2] a prosector in the Charité Hospital in Berlin, observed a spirochete in the blood of patients during the febrile stage of relapsing fever; though he did not publish this finding until 1873. In the Berlin epidemic of 1872–1873 there were over 100 fatal cases in the Charité Hospital alone, and hence abundant opportunity had existed to repeat the earlier observations. Others speedily confirmed Obermeier's findings but such was still the opposition to the acceptance of the " germ theory " that this early evidence of the etiologic relation of a pathogenic organism to a known fever was for a long time disputed and somehow never was granted the importance it merited. The causal relation of the organism to the disease was more definitely established when Munch, Moczutkowsky (1876), and Metchnikoff (1881) had shown that the injection of spirochetal blood is followed by characteristic relapsing fever in normal human adults.

In 1877–1878 Carter proved that the disease could be similarly transmitted to monkeys. In 1890 Pasternatzky found that the spirochete could live for some time in the body of a leech which had fed on a relapsing fever patient. From this it was an easy step to Tictin's experiments which showed the presence of spirochetes in bedbugs which had fed on relapsing fever cases. Tictin was able to transmit the disease to monkeys by injecting the fluid from crushed infected bedbugs. Though Flugge in 1891 had suggested that the louse might be a carrier of relapsing fever, proof of this was not furnished until a much later date. Sergent and his coworkers (1910–1911) and Nicolle and others (1912) infected monkeys with crushed lice which had been taken from cases of relapsing fever.

Another important advance in our knowledge of the disease occurred in 1904. For many years a fever of the East and West coasts of Africa, characterized clinically by well defined relapses and apparently due to the bites of ticks, had been known as African tick fever. In 1904 Ross and Milne found spirochetes in the blood of persons suffering with this disease, and Dutton and Todd confirmed that observation and showed that the organisms are transmitted by a tick, *Ornithodorus moubata.*

Since that time many other species of Argasine ticks of the genus *Ornithodorus* have been proved to serve as vectors of relapsing fever in various parts of the world. It has been shown moreover that a number of small animals may act as hosts to the parasite and so constitute a reservoir of the disease. From such animals the disease may be transferred to man by means of the tick as a vector. On the other hand, in epidemic relapsing fever transmission is probably direct from man to man by means of the louse or occasionally the bedbug. The relapsing fever of middle Europe and the Mediterranean littoral is of the louse-borne type, as is much of that of Asiatic countries. The African, Persian and Central American relapsing fever is for the most part carried by ticks.

[2] OBERMEIER, O.: Vorkommen feinster, eine Eigenbewegung zeigender Fäden im Blute von Recurrenskranken, Centralbl. f. d. med. Wissensch., 1873, xi, 145–147.

Have we since 1875 been spared further epidemics of relapsing fever because of our relative freedom from lice, or merely because no epidemic strain of the organism has developed in our midst? Certainly in our larger cities there are facilities for the transmission of a louse-borne disease sufficient to bring about limited outbreaks were the infection once started. Control measures should, however, guarantee us against a serious epidemic. Perhaps greater interest attaches to the possible spread northward of the infection in animals and ticks, from those central American countries in which it is prevalent. Ticks of the genus *Ornithodorus* are well distributed over our Southwest, and small animals to serve as a host reservoir are not lacking. The occurrence of four cases of relapsing fever in Texas [3] due to tick transmission shows that foci of infection already exist. In connection with the British Columbian outbreak, Hearle [4] published some very interesting observations which suggest that ticks are often transported to points far outside their usual range by attachment to migratory birds. It seems reasonable to expect therefore that in the United States we shall from time to time see sporadic cases of this disease in those people who are exposed to tick bites and that the number of such human cases will be proportionate to the prevalence of spirochetosis in the host animals and in the tick vectors. There exists, as to modes of transmission, a striking analogy between the rickettsial diseases, typhus and spotted fever, and relapsing fever. The gradual spread of the tick-borne Rocky Mountain spotted fever to distant states may be paralleled by relapsing fever.

These facts concerning a rare disease are perhaps of some interest to the internist who may be called upon to recognize it. If he should desire to consult a careful clinical description of the disease he will find that its more recent literature will be of comparatively little help to him in that respect. It is devoted far more to etiology than to symptomatology. A clearer impression of the clinical physiognomy of relapsing fever can be obtained from those who observed the disease with no distracting interest in spirochetes, lice or ticks. No better description can be found than that contained in the masterly article by William Pepper [5] based on the study and analysis of close to 200 cases seen in the wards of the Philadelphia Hospital during the epidemic of 1870.

VENEREAL DISEASE INFORMATION

FOR A NUMBER of years the U. S. Public Health Service has been publishing, for the information of physicians, health officers, and others, a monthly abstract journal known as "Venereal Disease Information." This

[3] WELLER, B., and GRAHAM, G. M.: Relapsing fever in Central Texas, Jr. Am. Med. Assoc., 1930, xcv, 1834–1835.

[4] HEARLE, E.: Vectors of relapsing fever in relation to an outbreak of the disease in British Columbia, Canad. Med. Assoc. Jr., 1934, xxx, 494–497.

[5] PEPPER, W.: Relapsing fever, *in* PEPPER, W., and STARR, L.: A system of practical medicine, 1885, Lea Brothers and Co., Philadelphia, pages 369–433.

publication contains usually one original article on a subject of general interest in connection with the venereal diseases and numerous abstracts from the current literature pertaining to these diseases. In the preparation of this abstract journal more than 350 of the leading medical journals of the world are reviewed and abstracts made of the articles on this subject.

The cost of "Venereal Disease Information" is only fifty cents per annum, payable in advance to the Superintendent of Documents, Government Printing Office, Washington, D. C. It is desired to remind the reader that this nominal charge represents only a very small portion of the total expense of preparation, the journal being a contribution of the Public Health Service in its program with State and local health departments directed against the venereal diseases.

REVIEWS

Child Guidance Clinics: A Quarter Century of Development. By GEORGE S. STEVENSON, M.D., and GEDDES SMITH. 186 pages. The Commonwealth Fund, New York. 1934. Price, $1.50.

Dr. Stevenson, as a director of the Division on Community Clinics of the National Committee for Mental Hygiene, has presented an excellent review of the development of Child Guidance Clinics since the establishment of the first clinic in Chicago in 1909. Since the beginning of the movement over two hundred such clinics have been established in this country, and as is well said by the authors, "The Child Guidance clinic is an attempt to marshal the resources of the community in behalf of children who are in distress because of unsatisfied inner needs or are seriously at outs with their environment. . . . Its service is rendered through the direct study and treatment of selected children by a team consisting of a psychiatrist (who is also a well trained pediatrician), a psychologist, and psychiatric social workers." Therefore, child guidance is essentially a medical problem, and the National Committee for Mental Hygiene has always attempted to keep this movement under medical control.

No better comment can be offered than that made in the last paragraph of the book: "The Child Guidance Clinic is more than a therapeutic agency. It is a tool for synthesizing the most promising approaches to problems of behavior and personality in childhood, and for demonstrating the synthesis to the professions concerned with these problems. It is a laboratory in which new leads may be found for the study of the child."

J. L. McC.

Who Shall Survive? A New Approach to the Problem of Human Relations. By J. L. MORENO, M.D. 437 pages. Nervous and Mental Disease Publishing Co., Washington. 1934. Price, $4.00.

The author presents what he calls sociometric case studies. He states: "A sociometric case study endeavors to give an accurate account how an individual or group grows and changes not as an individual or a group singled out but as a part of the community in which it is and not in metric relations only but through the widely ramified actual expressions of the interrelated subjects." There are many diagrams, percentage tables, and rather incomplete case histories. The book runs to 437 pages. The reviewer confesses it left him in a fog.

J. L. McC.

English-German and German-English Medical Dictionary. Part I. English-German. By JOSEPH R. WALLER, M.D., and MORITZ KAATZ, M.D. 201 pages; 11×15.5 cm. Franz Deuticke, Leipzig and Vienna. 1934. Price, M. 6.—.

The English-German part of this dictionary, by Dr. Moritz Kaatz, was written as a companion volume to the German-English Medical Dictionary of Dr. Joseph R. Waller. Brief yet reasonably complete for the more frequently used terms, this pocket-size dictionary should be useful to the student of medicine.

M. F. L.

Handbook of Physiology. By W. D. HALLIBURTON, M.D., and R. J. S. MCDOWALL, M.B., D.Sc. $xi + 971$ pages; 16.5×22 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1933. Price, $5.50.

Halliburton's *Handbook of Physiology* has been considered for years as a valuable text for medical students. In this thirty-third edition, Dr. McDowall has fol-

lowed the general plan of Professor Halliburton and has presented the subject in a clear and concise manner.

The introduction of blank pages at the end of each chapter, so that the student can make notes, is to be commended.

It is to be regretted, however, that references to original research publications are lacking.

F. A. R.

The Cyclopedia of Medicine. By GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. To be complete in 12 volumes; 9 volumes published to date. 19 × 26.5 cm. F. A. Davis Company, Philadelphia. 1931. Price, $120.00.

The first nine volumes of this monumental work have been issued and it is expected that the last three will be forthcoming within the next few months. The editors have arranged under the alphabetic system articles dealing with the fields of general medicine, surgery, gynecology and obstetrics, and the chief specialties. These subjects have been interpreted in a broad sense so as to include the underlying sciences on which our clinical knowledge is based. Though the general arrangement is alphabetical the alphabetic system is not followed in the same sense as it is in the dictionary. Many topics are dealt with under one main heading, and this heading only is placed alphabetically. For example, the section on cardiovascular diseases extends for nearly 400 pages in Volume 3 and constitutes in itself a rather complete monograph on this subject. In this same volume the article on the cerebrum and cerebellum takes up 150 pages. Similarly in Volume 8 the section on the liver and biliary tract occupies 231 pages. In Volume 6, 400 pages are devoted to hematology. These will serve as examples. In a sense, then, these volumes contain a group of longer sections on the chief fields of medicine, surgery and the specialties between which, according to alphabetic order, fall shorter articles on innumerable subjects.

The chief sections are the joint production of a number of authors. These authors have evidently been chosen with great care and in general may be said to be the leading authorities in the fields with which they deal. To cite only a few at random from the section on hematology: Rowntree on blood volume, Barcroft on hemoglobin, Peters on serum proteins, Bloor on lipides, Stadie on blood gases, etc. To the reviewer's mind these long sections contributed by so many notable authorities constitute the greatest attraction of the encyclopedia.

On the other hand it has not proved possible to confine all discussion of certain subjects under one heading. For example, there is a section on the lungs but it deals with only certain diseases of the lungs and with lung surgery, while such subjects as pneumonia and emphysema are dealt with elsewhere under the alphabetic order. It is evident that a careful General Index will be a necessity.

One feature of the encyclopediac arrangement lies in the inclusion of articles on many special topics concerning which the average physician's collection of books would contain little or nothing. Of this type are, for example, the careful articles on the causes of sudden death (37 pages), on deaf-mutism (12 pages), on immature and premature infants (38 pages), and many others. The excellent and full treatment of ophthalmological, otological and dermatological topics is notable. A serious attempt has been made to present in a brief form general reviews of the clinical sciences, under such headings as bacteriology, immunology, etc. The various subheadings under metabolism, each written by an author who has made important contributions to the subject he is discussing, are a good example of the value of these sections. The sections on pathological physiology are also very carefully done.

In general the articles on the infectious diseases, while for the most part adequate, appear disproportionately short in comparison to the space accorded to less common

conditions. Measles is dealt with in 13 pages and malaria in 16. Six pages are devoted to mumps, while the interesting article on monsters takes up 32 pages.

There appears also to be an excessive amount of space devoted to drugs, and in certain instances at least the discussion of the therapeutic usages of the drug should be revised to accord with modern practice.

The format of the volumes is excellent and the illustrations for the most part well reproduced, especially the cuts from drawings and photographs, which are used very freely. Certain of the colored illustrations are valuable; others are more striking than instructive.

The reviewer feels that the "Cyclopedia of Medicine" is a very valuable work and that for purposes of reference and general study it will prove an invaluable supplement to the library of any practicing physician. The Chief Editor and his Assistant and Associate Editors have performed an immense task in selecting the distinguished contributors to these volumes and in putting through the press so rapidly the nine volumes so far issued. The other volumes will be awaited with interest.

M. C. P.

COLLEGE NEWS NOTES

Nominating Committee for 1934–35

In accordance with the provisions of the By-Laws, President Jonathan C. Meakins appointed on May 5, 1934, the following Committee on Nominations:

Charles F. Martin, *Chairman*, Montreal, P. Q.
Roger I. Lee, Boston, Mass.
William J. Kerr, San Francisco, Calif.
Charles H. Cocke, Asheville, N. C.
Gerald B. Webb, Colorado Springs, Colo.

It is the duty of the Committee on Nominations "to nominate candidates for the elective offices, Board of Regents and Board of Governors. The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective states, provinces or districts which will be represented by the nominees, if elected. The list of nominees for President-Elect and for the first, second and third Vice-Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its annual business meeting. This does not preclude nominations made from the floor at the annual meeting itself."

By-Laws, Article I, Section 3.

Committee on Extension of Postgraduate Education

F. M. Pottenger, *Chairman*, Monrovia, Calif.
J. H. Musser, New Orleans, La.
Luther F. Warren, Brooklyn, N. Y.
Ernest B. Bradley, Lexington, Ky.
Walter L. Bierring, Des Moines, Iowa

The above Committee has been appointed by President Jonathan C. Meakins in accordance with the following resolution adopted at the meeting of the Board of Regents April 20, 1934:

> "*Resolved*, that the President appoint a Committee to investigate the advisability of and to formulate plans for the closer organization and greater cohesion of our members in their particular communities or states, such as done by the American College of Surgeons through their sectional meetings, with the object of carrying extension postgraduate medical educational facilities to physicians in more remote locations, and to bring back a report at the next meeting of the Board of Regents."

Gifts to the College Library

Acknowledgment is made of the following donations by members to the Library of the College by the authors:

Dr. Logan Clendening (Fellow), Kansas City, Mo.—1 book, "Behind the Doctor";

Dr. Mark Gerstle, Jr. (Associate), San Francisco, Calif.—1 book, "The Doctor Discusses Your Questions";

Dr. S. Calvin Smith (Fellow), Philadelphia, Pa.—1 book, "That Heart of Yours";
Dr. Felix Cunha (Associate), San Francisco, Calif.—6 reprints;
Dr. Merle Q. Howard (Fellow), Wauwatosa, Wis.—1 reprint;
Dr. Cole B. Gibson (Fellow), Meriden, Conn.—2 reprints;
Dr. Martin J. Synnott (Fellow), Montclair, N. J.—1 reprint;
Dr. William F. Wegge (Fellow), Milwaukee, Wis.—1 reprint;
Dr. Joseph Wiener (Associate), Asbury Park, N. J.—1 reprint;
Dr. David O. N. Lindberg (Fellow), Decatur, Ill.—6 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—2 reprints.

Dr. James S. McLester Honored

Dr. James S. McLester (Fellow), for many years a Regent of the American College of Physicians and a member of many important Committees of this organization, was selected as President-Elect of the American Medical Association at the last annual meeting of that Association at Cleveland.

Dr. Walter L. Bierring (Fellow and Regent of the College) was installed as President of the American Medical Association at the same session.

The Board of Trustees of the University of Pennsylvania recently created a second professorship of medicine and elected Dr. O. H. Perry Pepper (Fellow) to fill it. This is the first time in the 169 years of the history of the Medical School of the University of Pennsylvania that there has been provision for more than one professor of medicine. Dr. Alfred Stengel (Master), present professor of medicine, has been a member of the medical school faculty for 41 years, and although he has reached the age of retirement will continue for a period of three more years through an extension requested by the Trustees.

Dr. Frederick G. Banting (Fellow), for the past 11 years Professor of Medical Research at the University of Toronto School of Medicine, in recognition of his discovery of insulin, was knighted by King George of England on June 3.

Dr. Samuel E. Munson (Fellow), Springfield, Ill., addressed Perry and adjoining County Medical Societies June 8, on the subject of amebiasis. Dr. Munson, who has served as Councilor for the Fifth Councilor District of the Illinois State Medical Society for the past nine years, was reëlected for three years at the annual meeting of that society, held in Springfield, May 15 to 17

At the sixty-seventh annual session of the Mississippi State Medical Association at Natchez, May 8 to 10, the following members of the College contributed papers: *Fellows:* Dr. W. S. Leathers, Nashville, Tenn.; Dr. Henry Boswell, Sanatorium, Miss.; Dr. William Krauss, Meridian, Miss.; Dr. James S. McLester, Birmingham, Ala.; and Dr. G. W. F. Rembert, Jackson, Miss. *Associate:* Dr. Guy C. Jarratt, Vicksburg, Miss.

Dr. Howard L. Hull (Fellow) has resigned, effective July 1, as superintendent and medical director of Oakhurst Sanatorium, Elma, Washington, and has established an office in the Larson Building, Yakima, Washington, where he will enter private practice restricted to diseases of the chest. Dr. Hull was in charge of Oak-

hurst Sanatorium since September 1, 1923. His successor is Dr. Leslie P. Anderson of White Haven, Pa.

Dr. Lea A. Riely (Fellow and Governor for Oklahoma), Oklahoma City, as a guest of the Section on Medicine and Diseases of Children of the State Medical Association of Texas, delivered two addresses, "Diabetic Problems" and "The Diabetic Child," before the sixty-eighth annual session of the society at San Antonio, Texas, during the week of May 15.

Dr. Bernard L. Wyatt (Fellow) and the Wyatt Research Foundation is erecting in Tucson, Arizona, an ultra-modern building to house the Wyatt Clinic. The activities of the Clinic will be restricted to the field of arthritis.

Dr. D. F. Milam (Fellow), of the Rockefeller Foundation, New York City, has been assigned work in the Republic of Panama, and will be in Panama City for some months.

Dr. David Riesman (Fellow), Philadelphia, was the guest speaker at the 59th annual banquet of the Alumni Association of the School of Medicine, University of Cincinnati, on June 14. His subject was "Medical Progress in One Generation."

Dr. Harold G. F. Edwards (Fellow), Shreveport, La., addressed the Texas State Medical Association, San Antonio, May 15, on "Radiation Therapy in Malignant Diseases."

Dr. Hyman I. Goldstein (Associate), Camden, N. J., read a paper on "Hemorrhagic Blood Dyscrasias" before the New Jersey Medical Society at its 168th annual session, Atlantic City, June 6.

Dr. L. F. Barker (Fellow), Baltimore, read a paper on pneumonia before the same society on June 7, and the paper was discussed by Dr. Goldstein and Dr. Robert Kilduffe, of Atlantic City.

Dr. Ross V. Patterson (Fellow), for several years dean of the faculty of the Jefferson Medical College of Philadelphia, was recently appointed by the Board of Trustees of that institution as professor of therapeutics. The Alumni Association of Jefferson Medical College, at its 109th dinner early in June, presented the College with a bust of Dr. Patterson.

Dr. James E. Paullin (Fellow), Atlanta, Ga., was elected President-Elect of the Medical Association of Georgia at the recent annual session of that society at Augusta.

At the unveiling of the portrait of the late Dr. D. Bushrod James, former Professor of Gynecology at the Hahnemann Medical College, on April 20, Dr. James M. Anders (Fellow) made an address, representing the medical profession not connected with Hahnemann Medical College or Hospital.

Dr. James K. Hall (Associate) and Dr. Beverley R. Tucker (Fellow), both of Richmond, were elected President and Vice-President, respectively, of the recently organized Section on the History of Medicine of the Richmond Academy of Medicine.

Dr. Paul D. White (Fellow), of Harvard Medical College, Boston, recently delivered an address on heart disease to physicians of central Florida, under the auspices of the Orange County (Fla.) Medical Society.

Dr. J. O. Elrod (Fellow), Forsyth, Ga., has been elected Vice-President of the Monroe County (Ga.) Medical Society for the coming year.

Dr. Louis Hamman (Fellow), Baltimore, Md., is a Vice-President of the Medical and Chirurgical Faculty of Maryland for the coming year.

Dr. Robert A. Peers (Fellow), Colfax, Calif., was elected President-Elect of the California Medical Association at its annual meeting May 2.

Dr. Samuel E. Thompson (Fellow), Kerrville, Tex., was inducted as President of the State Medical Association of Texas at its annual meeting May 17.

The Seventh Annual Graduate Fortnight of the New York Academy of Medicine will take place October 22 to November 2, 1934. The program will be devoted to diseases of the gastrointestinal tract. Among Fellows of the American College of Physicians who will present subjects are:

Dr. Harlow Brooks, New York, N. Y.
Dr. A. C. Ivy, Chicago, Ill.
Dr. W. McKim Marriott, St. Louis, Mo.
Dr. Charles F. Tenney, New York, N. Y.
Dr. Arthur F. Chace, New York, N. Y.
Dr. William W. Herrick, New York, N. Y.
Dr. Walter A. Bastedo, New York, N. Y.
Dr. Thomas T. Mackie, New York, N. Y.

Dr. B. S. Pollak (Fellow), Medical Director of the Hudson County Tuberculosis Hospital and Sanatorium, Secaucus, N. J., has been appointed one of three to represent the United States at the Ninth Conference of the International Union Against Tuberculosis, to be held in Warsaw, Poland, September 4 to 6, 1934. He will discuss Professor Leon Bernard's paper on "The Use and Organization of Tuberculosis Dispensaries."

Dr. C. J. Tidmarsh (Associate), formerly of Montreal, is now connected with the Lahey Clinic, Boston.

Dr. William H. Walsh (Fellow), Chicago, assisted by Dr. Clarence O. Sappington, recently completed a survey of the Health Department of the City of Buffalo, upon the request of the Board of Health and the approval of the City Council of that City.

Dr. J. A. Myers (Fellow), Professor of Medicine at the University of Minnesota, and Dr. S. A. Slater (Fellow), Superintendent of the Southwestern Minnesota Sana-

torium, Worthington, have been elected Directors of the National Tuberculosis Association for the coming year.

Dr. Kennon H. Dunham (Fellow), Cincinnati, Ohio, has been elected President of the National Tuberculosis Association for the coming year.

Dr. Louis H. Roddis (Fellow), Commander (M. C.), U. S. Navy, is Editor of the U. S. Naval Medical Bulletin.

Dr. J. W. Torbett (Fellow), Marlin, Texas, was a delegate to the Texas State Medical Association at its recent meeting in San Antonio, and read a paper on "Our Biological Defenses or How Nature Cures."

OBITUARIES

DR. CLAUDE EDWARD CASE

Claude Edward Case, of Clifton Springs, N. Y., died at Doylestown, Pa., on January 27, 1934, of lymphosarcoma. Dr. Case was born at Doylestown in 1893 and received his early education in the public schools there. He attended the medical department of the University of Pennsylvania from which he was graduated in 1917. After serving an internship in the Philadelphia General Hospital he became a lieutenant in the Medical Corps of the United States Army and was stationed at various American camps during the World War. Following his discharge from the army he associated himself with the health service of Cornell University at Ithaca and became Assistant Professor of Hygiene. In 1927, Dr. Case joined the staff of the Clifton Springs Sanitarium and Clinic. He was a member of Phi Chi medical fraternity, the New York State Medical Society, and the American Medical Association, and on February 10, 1930, he was made a Fellow of the American College of Physicians.

During recent years Dr. Case was particularly interested in the relation of radiology to internal medicine and published several papers in that field. He was known as an unusually kindly physician, one to whom his parents were devoted. For recreation he enjoyed golf and was an accomplished pianist. Dr. Case is survived by his widow, Emily Radcliffe Case.

DR. WARREN B. STONE

Dr. Warren B. Stone (Fellow), Schenectady, N. Y., died March 31, 1934, following a stroke.

Dr. Stone was born in Lynn, Mass., in 1876. He received his medical training at Harvard University Medical School, from which he graduated in 1899. Thereafter, he served as intern for a year and a half at St. Luke's Hospital, New Bedford, Mass., and then sought postgraduate study at the University of Berlin. He also did postgraduate work at Albany Medical College and Union University. In 1916, he became Head of the Ellis Hospital Pathological Laboratory. During the World War, Dr. Stone was commissioned a Captain, but his services were retained in this country rather than abroad, due to his work in controlling the influenza epidemic. It is said that a serum developed by Dr. Stone at the Ellis Hospital was very effectively used in controlling the spread of influenza, and that only 1 per cent of the 25,000 to whom the serum was administered contracted the disease.

At the same time that Dr. Stone held the position as Head Pathologist of the Ellis Hospital, his ability was also recognized by the county authori-

ties, who made him head of the county pathological work. This laboratory, under his effective administration, became one of the divisional laboratories of the State Department of Health. In 1923, Dr. Stone resigned from his post at the Ellis Hospital to devote his full time to practice and consultation work. He fitted out a private diagnostic laboratory in his home with all modern equipment. During the past two years, he also did the pathological work at the Glenridge Sanatorium. He was also Examiner in Serology for the Civil Service Commission of the City of New York.

Dr. Stone was a past president of the New York State Pathological Society, a member of the Schenectady County Medical Society, the New York State Medical Society, the New York State Society of Pathology and Public Health, and had been a Fellow of the American College of Physicians since 1916.

DR. ADDISON E. ELLIOTT

Dr. Addison E. Elliott (Fellow) of San Diego died April 9, 1934. Dr. Elliott was ill last January with a pulmonary edema for a couple of weeks; recovering from that he worked practically all the time until two days before death occurred.

Dr. Elliott was born in 1875. He received his medical education at Rush Medical College. The first years following were spent in Chicago. About 1914 Dr. Elliott moved to El Centro, California, where he built up a good diagnostic and surgical practice. At a period after the War Dr. Elliott gave up his other work for roentgenology, in which he had been interested for many years, and went to San Diego. Following a year's work in roentgenology at the San Diego County Hospital he became associated with Dr. Lyell Kinney, with whom he carried on in the active work of roentgenology until his death.

Dr. Elliott was made a Fellow of the College in 1930. He was at one time President of the University Club and had been Chairman of the Council of the San Diego County Medical Society, and President of the San Diego Academy of Medicine, in addition to having memberships in other scientific organizations.

Dr. Elliott was a kindly man. He had no malice in his heart but thought kindly of all worthy men. He went out of his way to do acts of kindness that endeared him to all with whom he came in contact. Though he was modest and by nature moderately retiring he took his responsibility as it came to him, meeting his problems with clear decision. He had many friends in the profession in California. In San Diego, his home, he was loved as are all kindly, able men. His death was a loss to the profession and his community.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Governor for Southern California.

DR. HENRY GREEN

Dr. Henry Green of Dothan, Alabama, an Associate of the College, died, after a short illness, on February 22, 1934, of cerebral hemorrhage.

Dr. Green was born in 1867 and received his M.D. degree from the University of Alabama School of Medicine in 1892. He practiced in Dothan, Alabama, up to the time of his death. Dr. Green was past President of the Houston County Medical Society and also of the Medical Association of the State of Alabama. For many years Dr. Green did a very large practice in his community.

He was beloved as a physician and admired as a man. He was honest, high-minded, intelligent, and sympathetic. In his private life, as well as his professional life, Dr. Green was an ideal citizen. He was active until about two days before his death and his passing is a loss to the American College of Physicians as well as to the medical profession.

FRED WILKERSON, M.D., F.A.C.P.,
Governor for Alabama.